Manual of Operations
For
Therapeutic Clinical Trials

Clinical Research Management Branch (CRMB)
Therapeutics Research Program

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

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A. INTRODUCTION

Welcome to the Division of AIDS (DAIDS).

The DAIDS, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), is the sponsor for these clinical trials. The Clinical Research Management Branch (CRMB), Therapeutics Research Program (TRP), DAIDS, is available to help your clinical site/center successfully conduct these trials. CRMB's role includes:

- Managing a comprehensive portfolio of grants, cooperative agreements, and contracts to implement all aspects of clinical trials research;
- Helping site staff understand their responsibilities for ensuring that the research is of high quality and conducted in accordance with all applicable regulations and guidelines;
- Developing procedures for the management of clinical sites/centers.
- Providing each clinical trials program with resources for developing study protocols, coordinating program-wide communication, and monitoring the performance of individual sites and the program as a whole; and identifying factors negatively affecting program performance and addressing these problems in collaboration with the program's leadership.

This reference manual is designed to provide your site/center with the information necessary to administer your clinical trials programs. It first explains the procedures that staff shall follow to establish clinical sites and pharmacies, and to ensure the quality of their study data. Next, an overview of the site monitoring process is provided. Following this, working instructions are presented regarding enrolling prisoners as volunteers, closing sites/centers, storing clinical trials records, and providing informed consent, etc. A listing of CRMB staff to contact for further information is also presented.

Be sure to check the Web page for your collaborative group to obtain additional information on group policies, procedures, organization, and resources.

If you have any questions or comments about this reference manual, please contact:

Clinical Research Management Branch
TRP/DAIDS/NIAID/NIH
6700-B Rockledge Drive, MSC 7624
Bethesda, Maryland 20892
(301) 496-8124

B. DAIDS/TRP/CRMB MISSION

B.1. Division of AIDS

The mission of the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), is to increase basic knowledge of the pathogenesis, natural history and transmission of the Human Immunodeficiency Virus (HIV), and to promote progress in its detection, treatment, and prevention.

The DAIDS accomplishes its mission by planning, funding, implementing and evaluating grants, cooperative agreements, and contracts in the following areas: 1) basic and clinical research; 2) discovery and development of therapies for HIV infection and its complications; 3) discovery and development of vaccines and other preventive interventions; and 4) training of researchers.

B.2. Therapeutics Research Program

The Therapeutics Research Program (TRP) of the DAIDS has responsibility for oversight and evaluation of the DAIDS-funded therapeutic clinical trials research programs. These programs include multiprotocol, multicenter cooperative groups performing clinical trials in adults and children, single-protocol cooperative groups, and single-site trials. They take place at hundreds of clinical sites/centers throughout the United States and in other countries. The TRP also has responsibility for oversight and evaluation of programs for drug discovery and pre-clinical evaluation.

The TRP identifies scientific priorities and needs, and develops new initiatives, including: 1) access to clinical trials for under-served populations which address the changing demographics of HIV disease, and 2) the research needs identified in consultation with voluntary and professional health organizations, including community-based organizations and health care providers. Working with other Government agencies and other components of the NIH, the TRP identifies the need for and prepares training initiatives specifically required for HIV therapeutic clinical trials efforts and coordinates the DAIDS research efforts regarding special population groups. The TRP evaluates operations of the clinical trials sites/centers, makes recommendations and provides assistance as necessary.

B.3. Clinical Research Management Branch

The Clinical Research Management Branch (CRMB) of the TRP develops, implements, and evaluates a program of research grants, cooperative agreements, and contracts to conduct HIV therapeutic clinical trials. The program components include clinical sites/centers, as well as statistical and data management centers, a site monitoring contractor, and operations centers to develop study protocols and provide logistical support to clinical trial investigators. The CRMB also manages the fiscal resources supporting these programs.

As necessary, to ensure the successful completion of the research agenda, CRMB staff coordinate the efforts of clinical trials investigators, other DAIDS components (e.g., Pharmaceutical Affairs Branch, Regulatory Affairs Branch), other components of the NIH (e.g., other Institutes, Fogarty International Center), and other Government agencies concerned with HIV therapeutics clinical research.

Structure, Oversight and Financial Support of the Therapeutic AIDS Clinical Trials Groups

Executive Branch of the Federal Government

Cabinet

- Department of Agriculture
- Department of Commerce
- Department of Defense
- Department of Education
- Department of Energy
- **Department of Health and Human Services**
- Department of Housing and Urban Development
- Department of Interior
- Department of Justice
- Department of Labor
- Department of State
- Department of Transportation
- Department of Treasury
- Department of Veterans Affairs

Department of Health & Human Services (DHHS)

Major Organizations

- Administration on Aging (AoA)
- Administration for Children and Families (ACF)
- Agency for Toxic Substances and Disease Registry (ATSDR)
- **Centers for Disease Control and Prevention (CDC)**
- **Health Care Financing Administration (HCFA)**
- Agency for Health Care Policy and Research (AHCPR)
- **Food and Drug Administration (FDA)**
- **Health Resources and Services Administration (HRSA)**
- Indian Health Service (IHS)
- **National Institutes of Health (NIH)**
- **Office for Human Research Protections* (OHRP)**
  Formerly the Office for Protection from Research Risks (OPRR)
- Substance Abuse and Mental Health Services Administration (SAMHSA)

Office for Human Research Protections (OHRP)

Responsible for developing and implementing all regulations (45CFR46), policies, and procedures related to the **protection of human subjects in research** conducted or supported by DHHS.

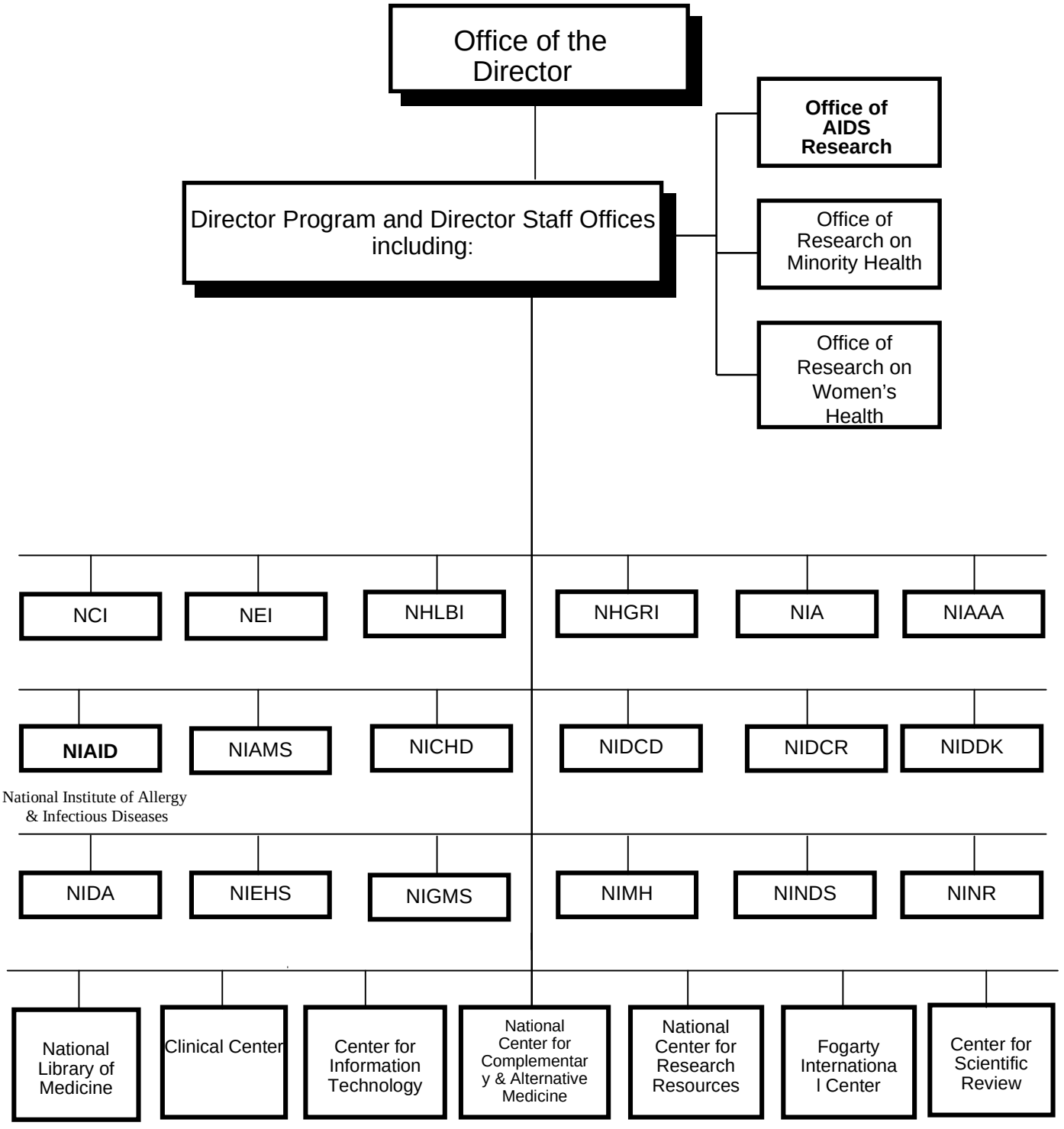
Includes requirements for:

1. Informed consent

2. IRB

3. Participation of special populations (e.g., pregnant women, fetuses, children, and prisoners)

National Institutes of Health (NIH)



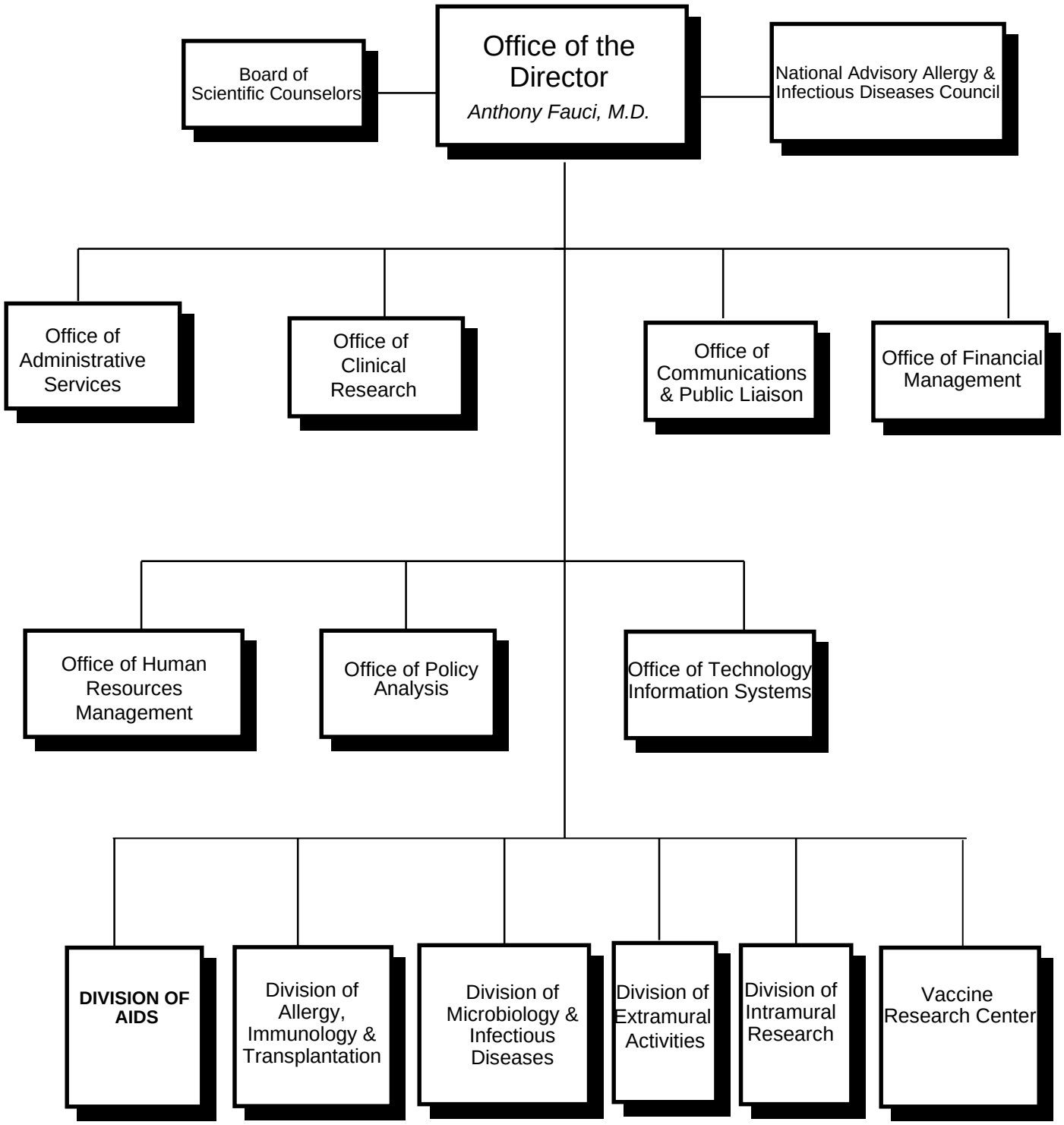
Office of AIDS Research (OAR)

- Responsible for the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program.

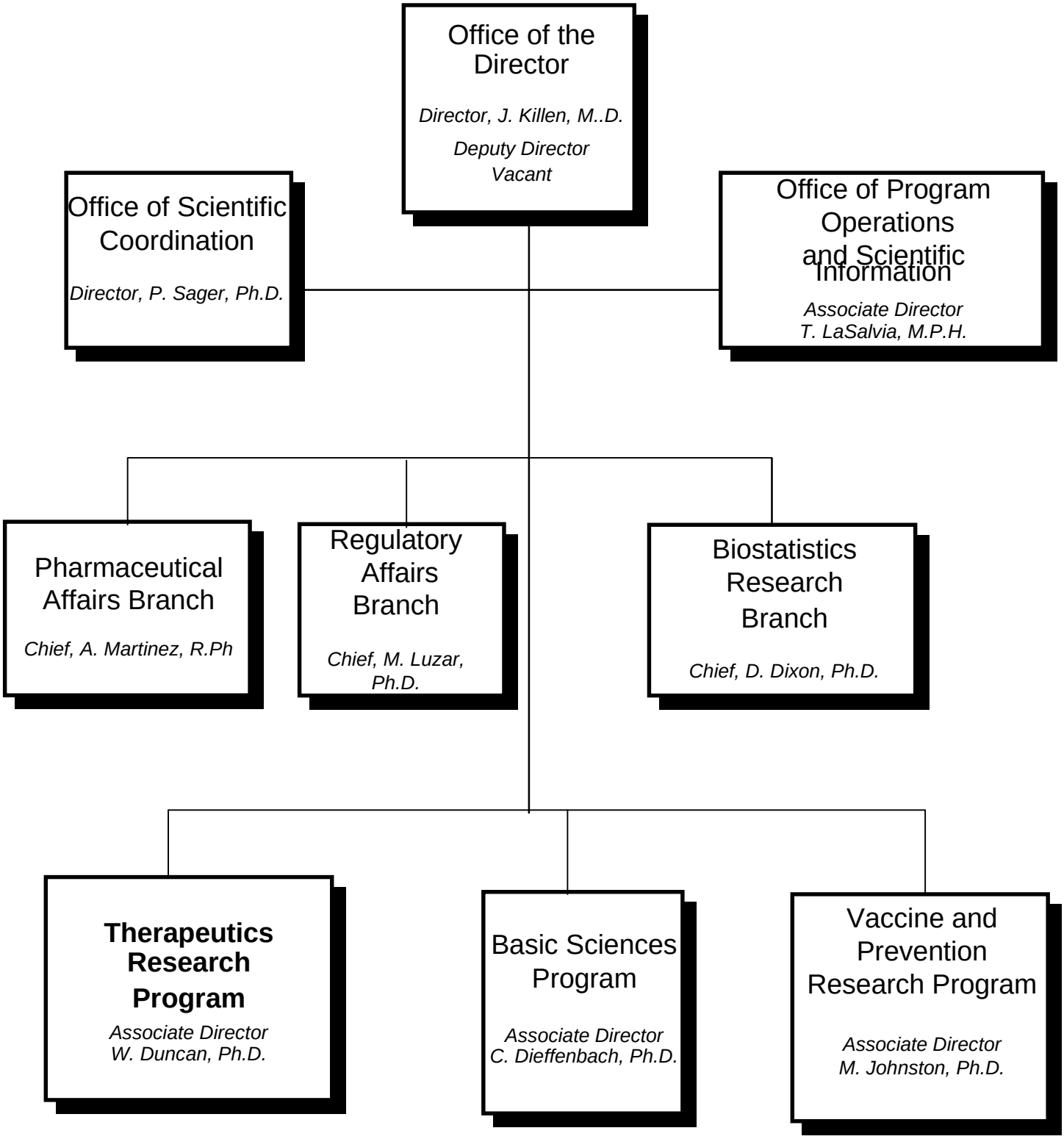
- Authority to plan, coordinate, evaluate and fund all NIH AIDS research.

- Responsible for developing annually, a comprehensive plan and budget for all NIH AIDS research.

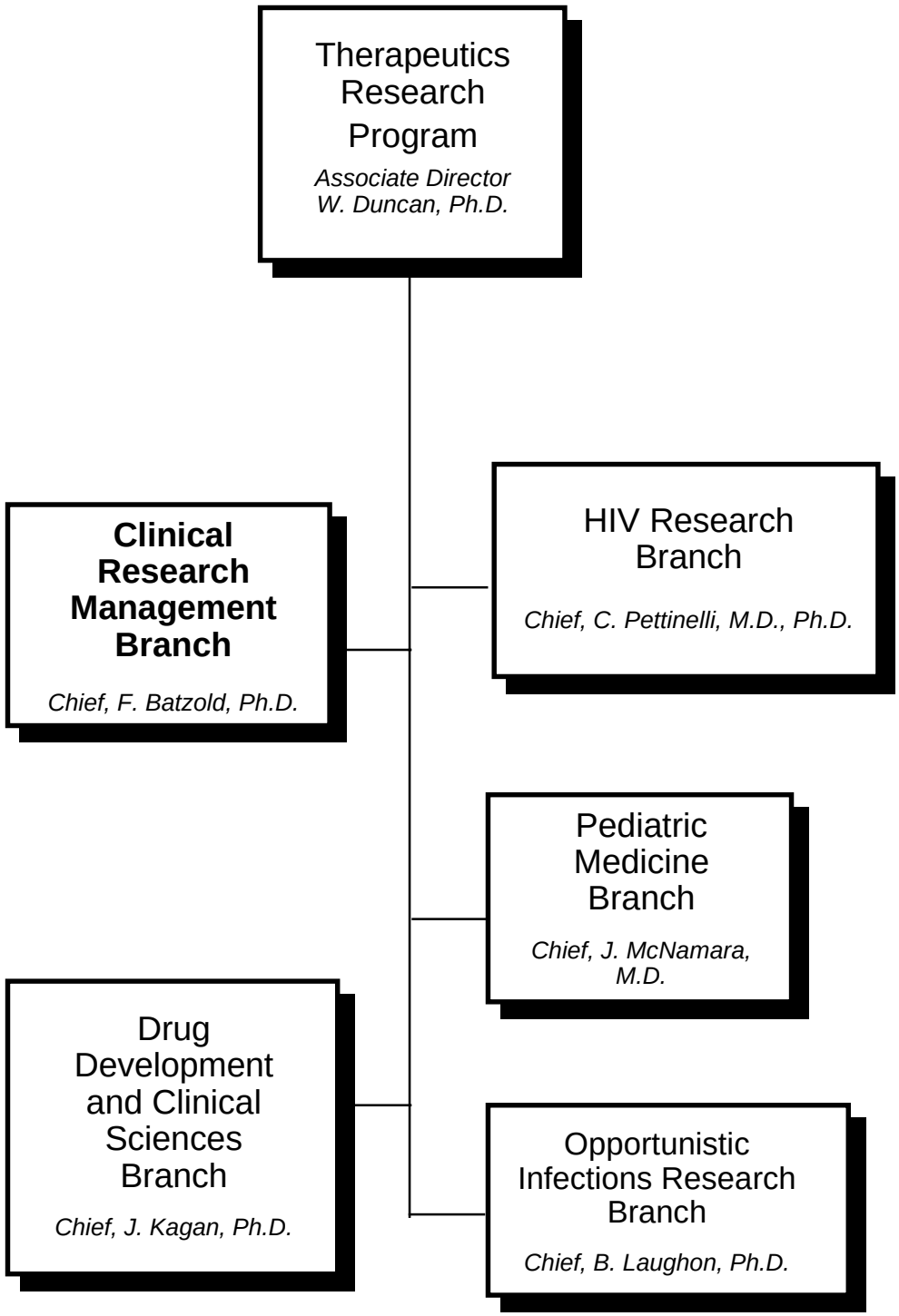
National Institute of Allergy & Infectious Diseases (NIAID)



Division of AIDS (DAIDS)



Therapeutics Research Program (TRP)

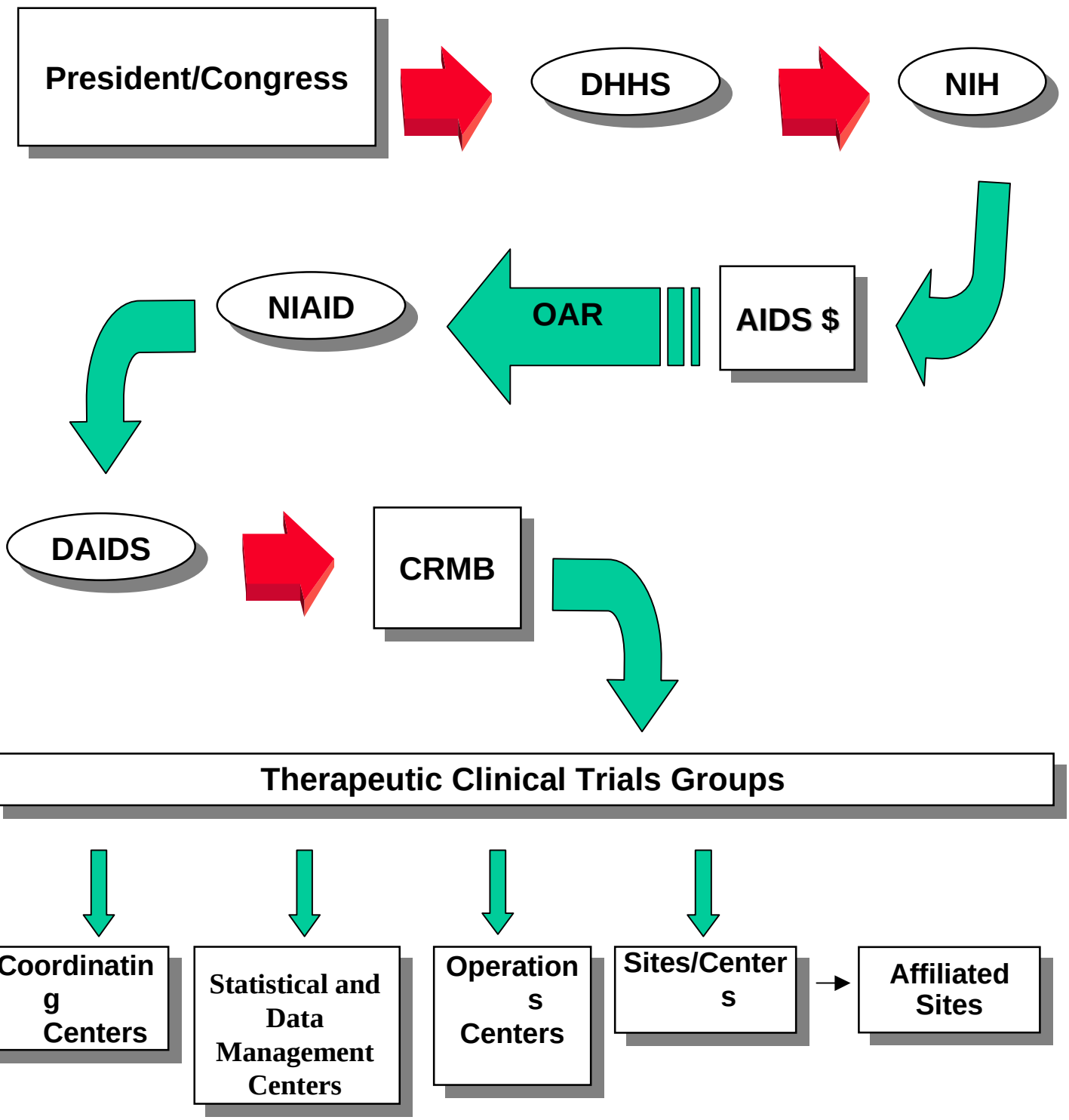


TRP

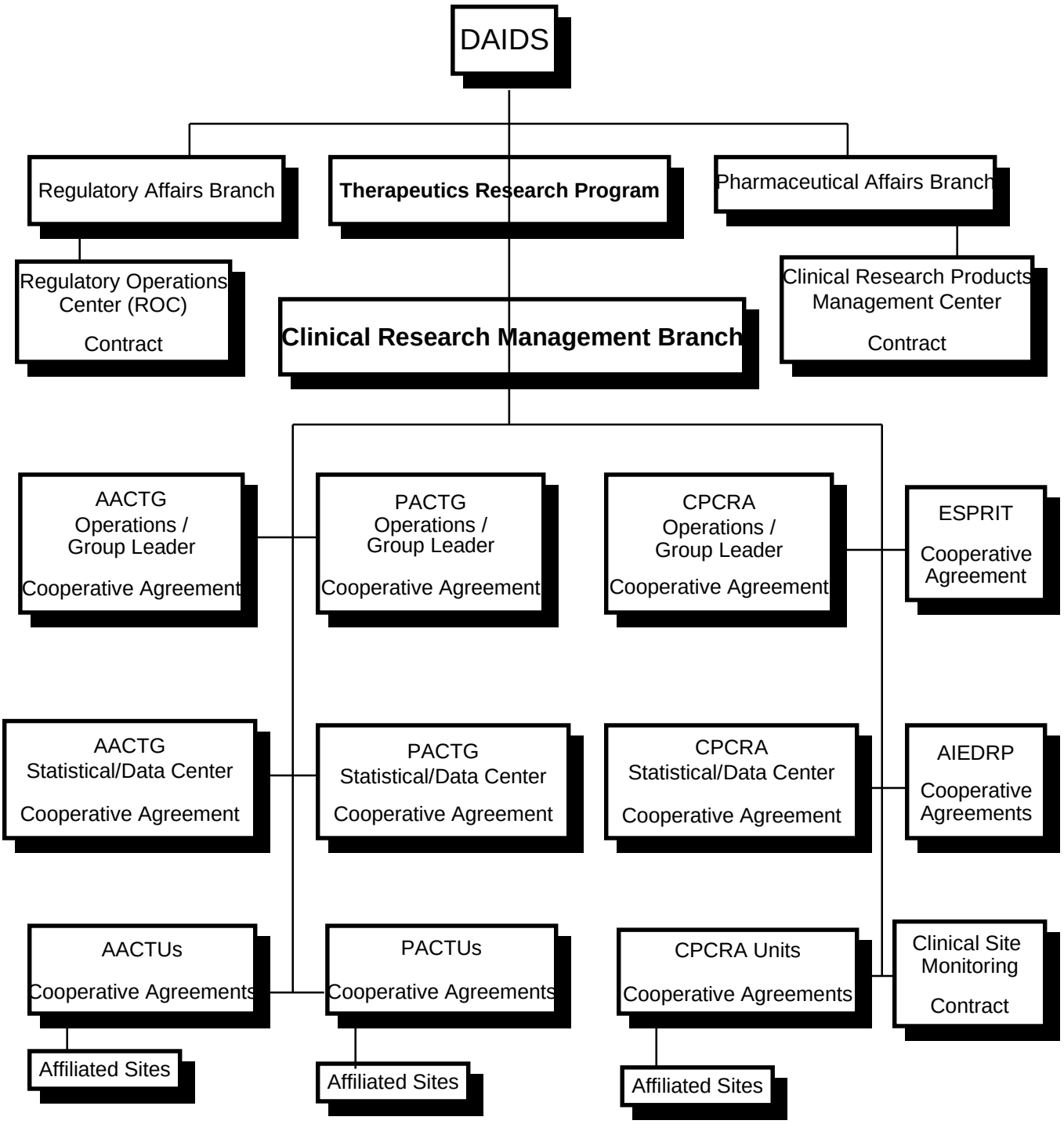
The Therapeutics Research Program (TRP) is responsible for the following major programs:

- **Acute Infection and Early Disease Research Program (AIEDRP)**
- **Adult AIDS Clinical Trials Group (AACTG)**
- **Evaluation of Subcutaneous Proleukin® in a Randomized International Trial (ESPRIT)**
- **National Cooperative Drug Discovery Groups--OI (NCDDG)**
- **Pediatric AIDS Clinical Trials Group (PACTG)**
- **Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)**

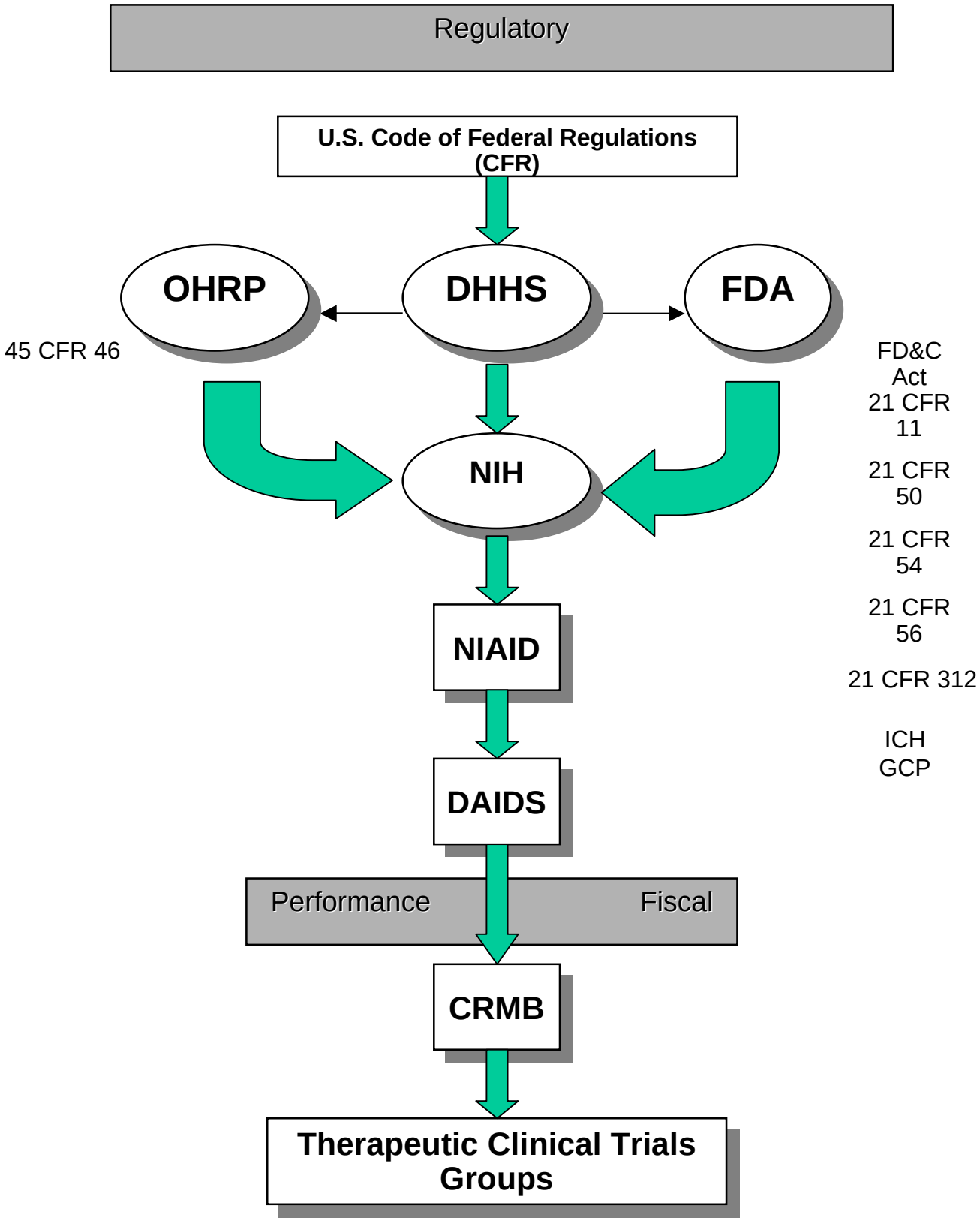
Financial Support



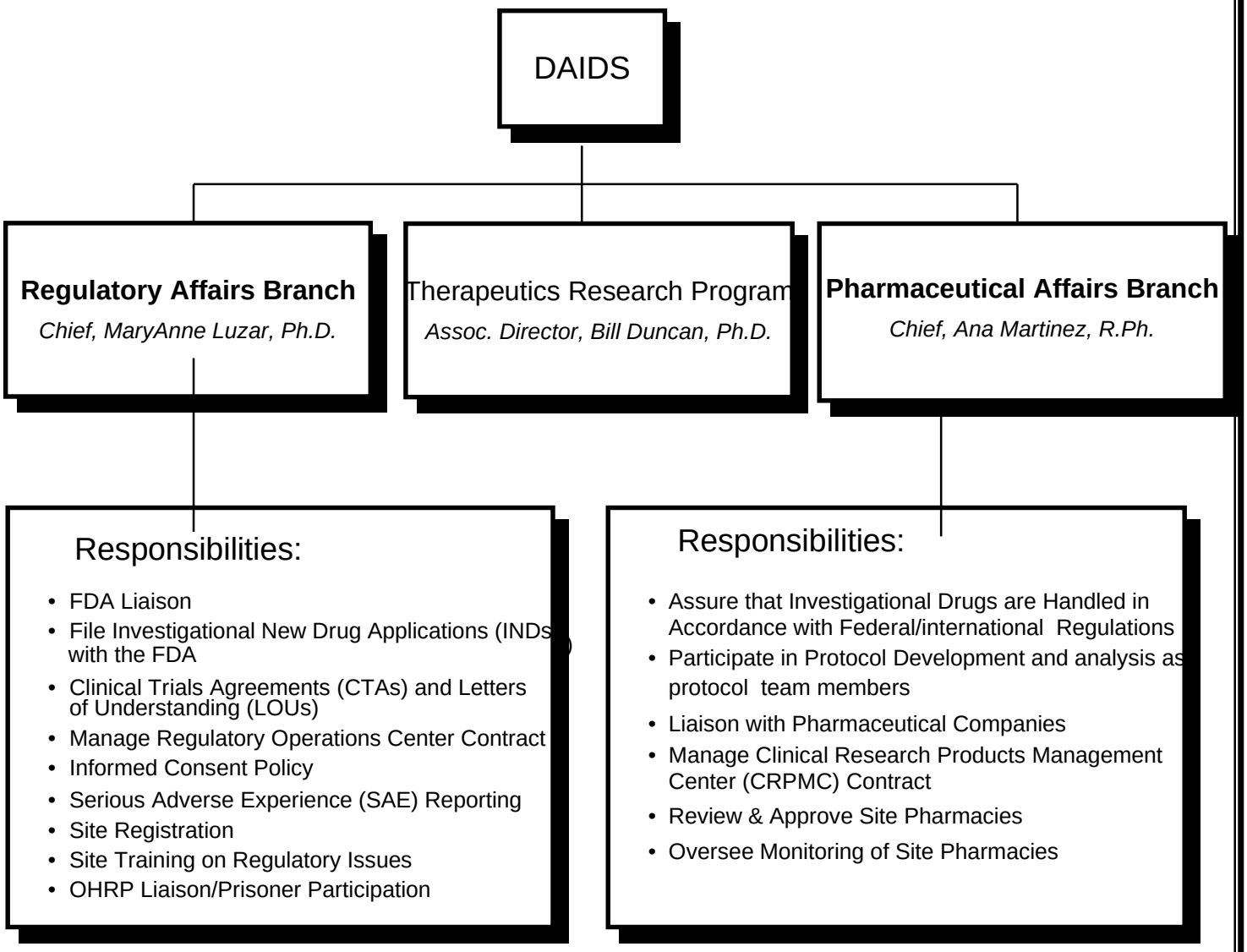
TRP Financial Support



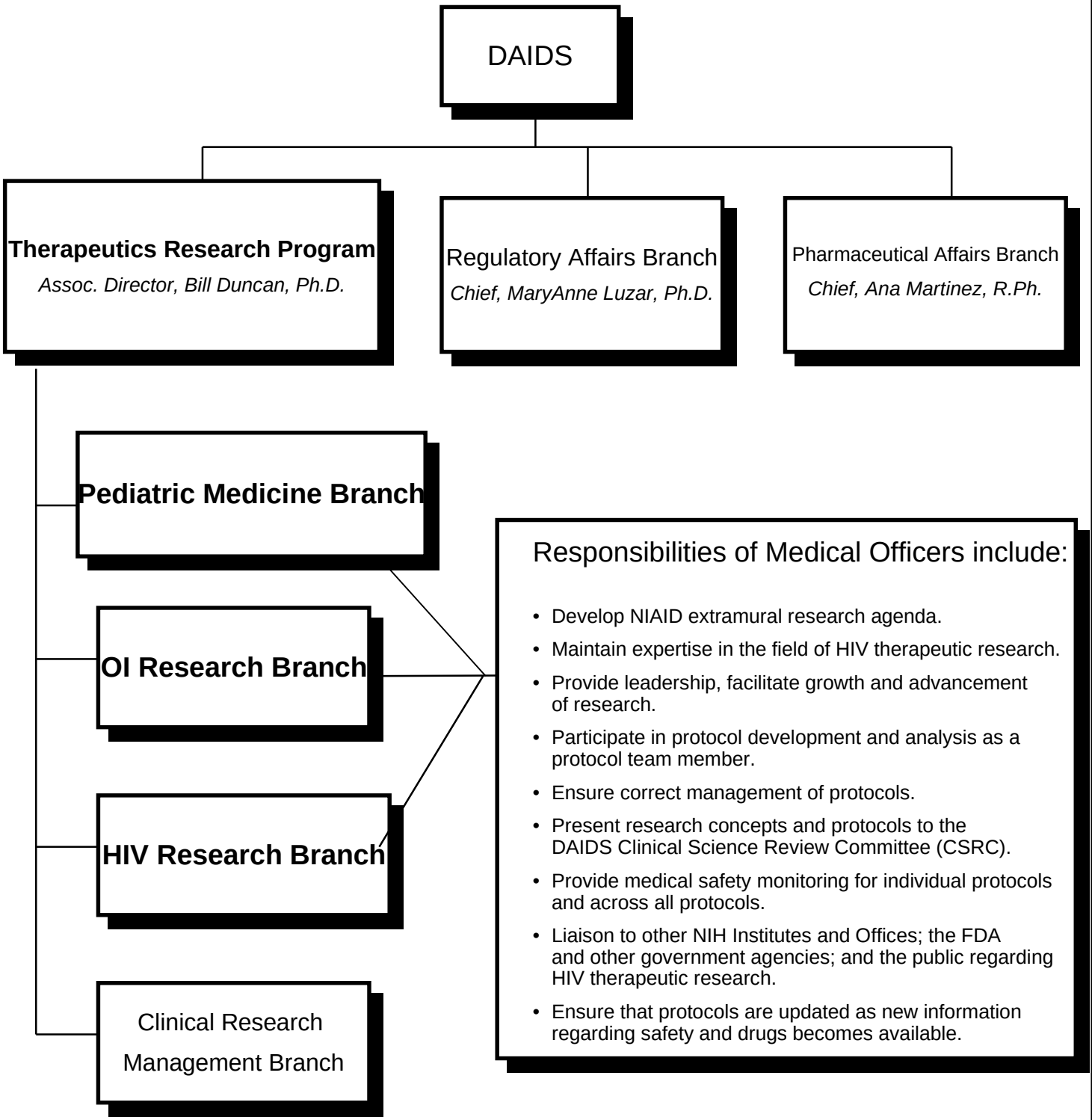
Oversight


Regulatory
U.S. Code of Federal Regulations (CFR)
OHRP
DHHS
FDA
45 CFR 46
FD&C Act
21 CFR 11
21 CFR 50
21 CFR 54
21 CFR 56
21 CFR 312
ICH GCP
NIH
NIAID
DAIDS
Performance
Fiscal
CRMB
Therapeutic Clinical Trials Groups

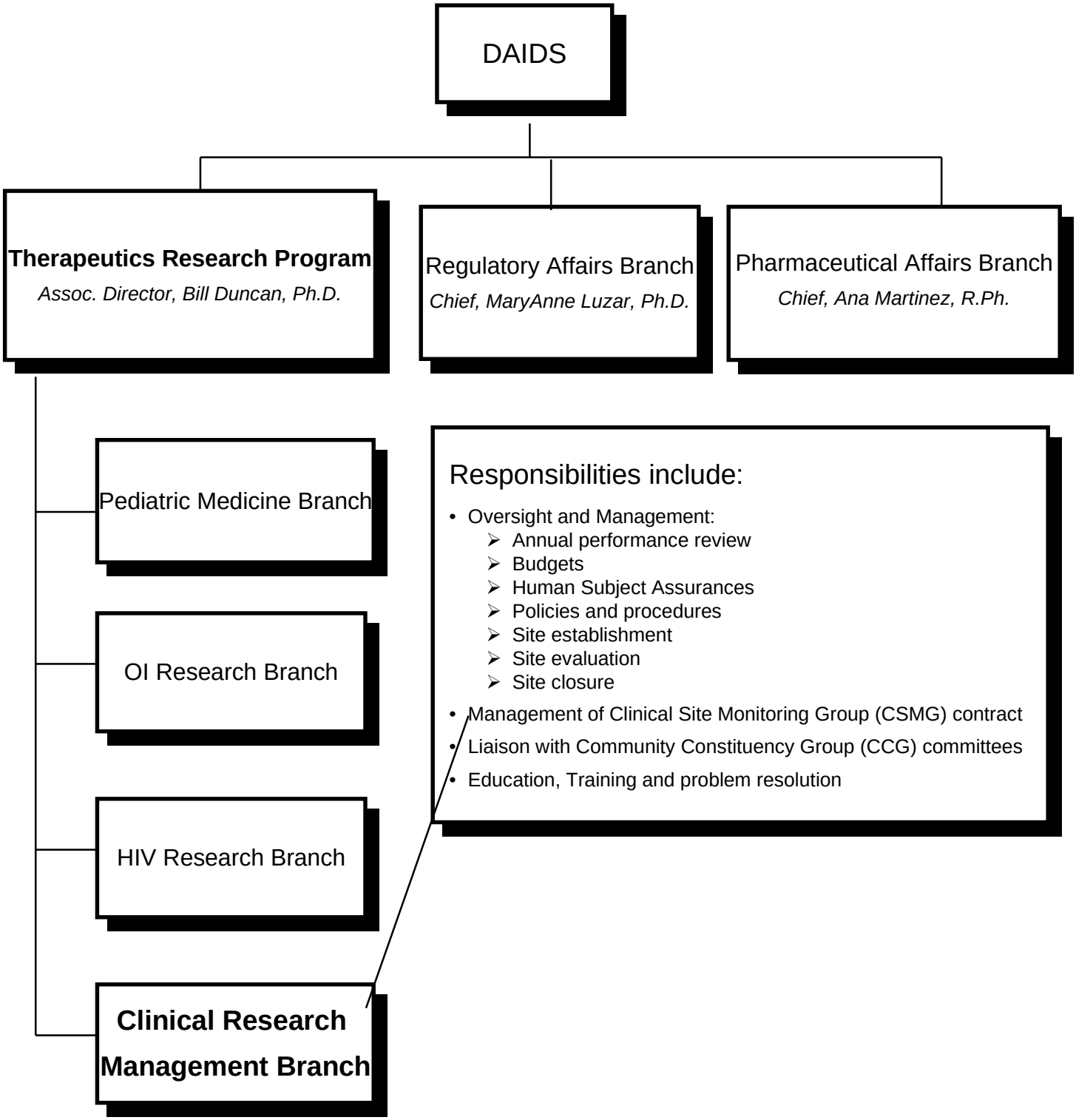
RAB & PAB Responsibilities

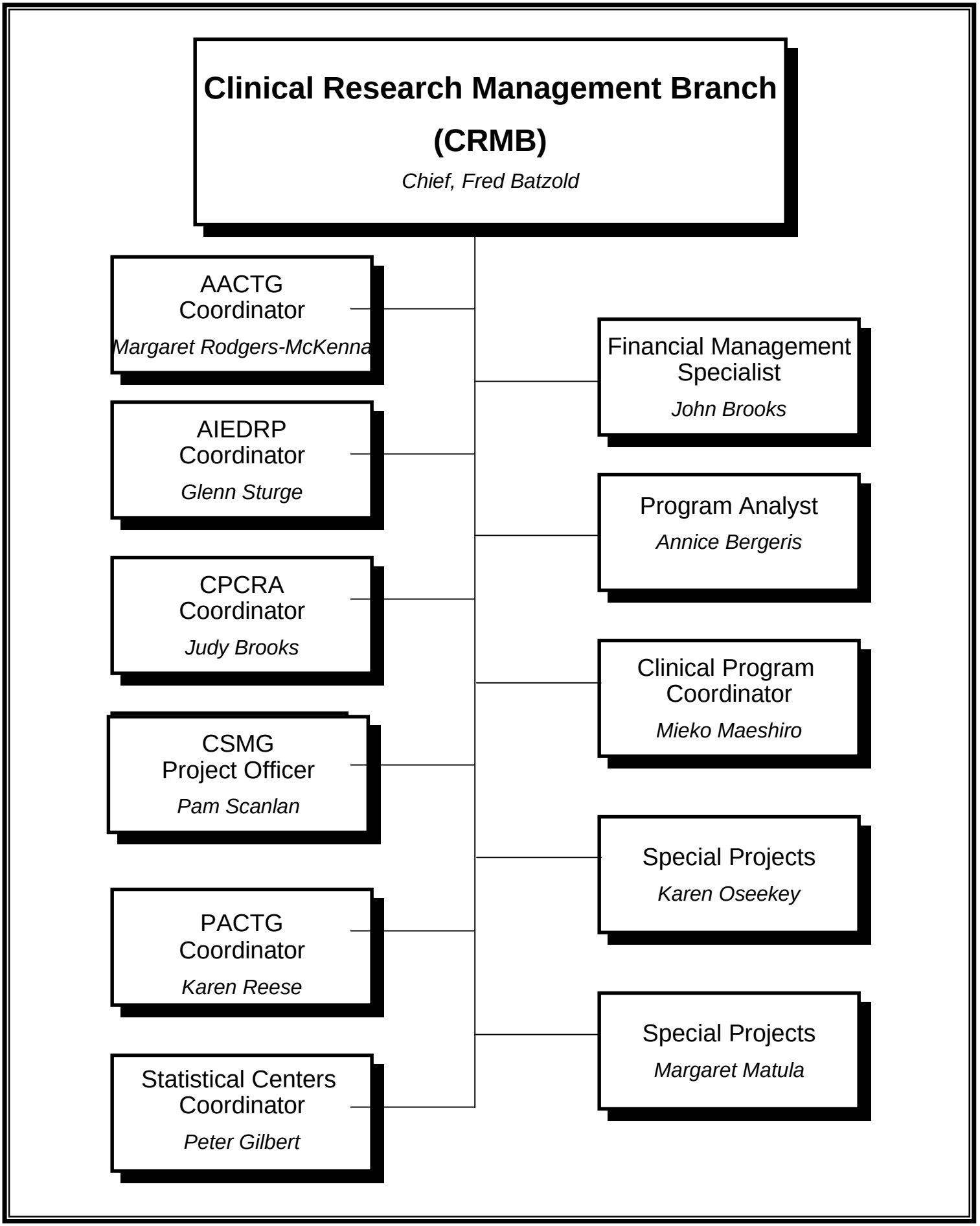


TRP Responsibilities



TRP Responsibilities




Clinical Research Management Branch
(CRMB)
Chief, Fred Batzold
AACTG Coordinator
Margaret Rodgers-McKenna
AIEDRP Coordinator
Glenn Sturge
CPCRA Coordinator
Judy Brooks
CSMG Project Officer
Pam Scanlan
PACTG Coordinator
Karen Reese
Statistical Centers Coordinator
Peter Gilbert
Financial Management Specialist
John Brooks
Program Analyst
Annice Bergeris
Clinical Program Coordinator
Mieko Maeshiro
Special Projects
Karen Oseekey
Special Projects
Margaret Matula

D. BUDGET/GRANT PROCEDURES

CARRYOVER PROCESS

The use of un-obligated funds remaining in a grant account at the end of a budget period is at the discretion of NIAID. A programmatic evaluation will determine the best use of the funds, which may include consideration of a carryover request. Carryover is not automatic in a cooperative agreement (U01). If funds remain at the end of the grant year, the grantee may formally request a carryover of all or a portion of these funds. NIAID will consider the request based on a well-justified need. Each carryover request is considered separately.

NIAID will not consider a carryover request until the Financial Status Report (FSR) (OMB Form 269) is received from the grantee after verifying that funds remain in the grant account. The FSR is due 90 days after the end of the budget period.

The formal carryover request must:

1. Specify the amount to be carried over.
2. State the reason the funds remain un-obligated.
3. State how the funds will be spent; show direct costs, facilities and administrative costs, and provide a line item budget using the budget pages from a PHS 2590 form.
4. Explain the impact the use of the funds will have on the project.
5. Be signed by both the PI and an institutional official.
6. Be submitted to the Grants Management specialist and copied to the CRMB representative.

NIH recommends that grantees use e-mail to send administrative requests requiring approval, such as: change in PI, transfer of substantive programmatic work, reductions in effort, no-cost extensions, carryover of funds, and significant re-budgeting. For more information and advice, see the notice in the NIH Guide at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-009.html.

KEY PERSONNEL CHANGES

Per the administrative terms included in the NGA:

If, for any reason, the Principal Investigator should change during the time of this contract, prior notification in writing must be given to the NIAID Program Coordinator for approval of a replacement. In addition, NIAID must be notified of any anticipated changes of a Subunit Principal Investigator, Clinical Coordinator (if applicable), Pharmacist, Study Coordinator, or other key personnel.

NONCOMPETING CONTINUATION APPLICATION

The Type 5 application is due 60 days before the end of the current budget period. Approximately 2 months before the due date, CRMB will send out a letter detailing the requirements for this application and the Total Cost Dollars available.

NOTICE OF GRANT AWARD (NGA)

The NGA includes:

1. A cover letter with general information
2. Section I - Detailed award data including a categorical breakdown and recommended future year total cost support
3. Section II - Payment/hotline information
4. Section III - Administrative terms and conditions of award

The administrative terms and conditions of award include details specific to this award including any restrictions, reasons for corrections, offsets, or carryover information. If there is a restriction, it may also include instructions on what is needed to remove the restriction.

RE-BUDGETING

Re-budgeting of funds within a grant year may be done at the discretion of the Principal Investigator without prior approval by NIAID with two exceptions.

1. No funds may be moved in or out of the subject care category.
2. Significant re-budgeting, whether or not the particular expenditure(s) requires prior approval under rules governing budget changes. Significant re-budgeting occurs when expenditures in a single direct cost budget category deviate (increase or decrease) from the categorical commitment level established at the time of the competing award by more than 25 percent of the total costs awarded.

E. SITE/CENTER ESTABLISHMENT

E.1. Site/Center Establishment Process

The principal investigator (PI) at each clinical site/center participating in Division of AIDS (DAIDS)/Therapeutics Research Program (TRP) sponsored research is the primary individual responsible for establishing a clinical research site/center and ensuring that the site is staffed with qualified individuals experienced in the conduct of clinical trials research. The responsibilities also include establishment of internal policies and procedures that are in keeping with the Code of Federal Regulations (CFR) and Good Clinical Practice (GCP) Guidelines to protect research subjects and produce reliable study information.

E.2. Site/Center and Pharmacy Establishment Requirements

Site and pharmacy establishment information is to be submitted to the Clinical Research Management Branch (CRMB) Program Coordinator when a new site/pharmacy is initially opened. Site and pharmacy plans are also to be submitted for any additional affiliated sites.

Two important activities must take place before a new site/center may register for any study protocol: 1) Site Establishment and 2) Pharmacy Establishment.

Site/Center-Pharmacy establishment is required for all clinical sites/centers conducting research studies for which the DAIDS holds the Investigational New Drug Application. For other studies, site/center pharmacy establishment may be required as deemed necessary by DAIDS.

The site establishment form and pharmacy plan provide DAIDS/TRP with important personnel and clinical site information that assists with communication between the clinical sites/centers and DAIDS during the project period. All sites/centers must be established before protocol registration can take place.

The site establishment form is to be submitted to the appropriate CRMB Program Coordinator when a new site is opened or when key personnel changes occur during the project period. The pharmacy plan is to be submitted to the Chief of the Pharmaceutical Affairs Branch

Key Personnel are the PI, study coordinator, and pharmacist of record at the clinical research site/center and any affiliated sites/centers. Usually, those individuals named on the site establishment and pharmacy plans are considered to be key personnel.

For purposes of site/center establishment, key personnel are considered to be the PI, study coordinator and pharmacist at the clinical site/center and any affiliated sites/centers.

E.3. Affiliated Sites/Centers

Affiliated sites/centers may only be established if:

1. The Clinical Research Management Branch and the Clinical Trials Group of which the sponsoring site/center is affiliated have given approval.
2. The sponsoring clinical site/center has demonstrated the capability to effectively conduct clinical trials and has met all performance standards that have been set by the respective clinical trials group.
3. The site/center has the appropriate staff that has time to provide oversight and guidance to the affiliated site/center staff.
4. At least ten subjects will be actively followed on-study each year at the affiliated site/center.
5. A separate site/center Establishment Form and Pharmacy Plan are required for each site/center and each affiliated site/center.

NOTE: New sites/centers will not be approved during the final year of a project period.

F. CLINICAL RESEARCH SITE/CENTER MANAGEMENT

F.1. Policy

All national and international clinical research sites/centers participating in studies sponsored by DAIDS are required to develop and maintain a management plan that describes the ongoing management and assessment of the clinical research activities.

F.2. Responsibility

As stated on the Food and Drug Administration (FDA) Form 1572, the Principal Investigator (PI) assures that the investigator will personally conduct or supervise the clinical trial, and maintain accurate and complete research records.

To ensure compliance with other Federal and associated regulations and guidelines, the DAIDS requires that:

A. The PI accepts ultimate responsibility for the quality of the data, subject safety, protocol adherence for all NIAID sponsored studies conducted at their sites/centers and the overall function of the clinical research site/center.

B. The PI agrees to: 1) conduct the study/studies in accordance with the current protocol and standards of Good Clinical Practice (GCP), 2) be responsible for obtaining an Institutional Review Board (IRB)/Ethics Committee (EC) approval for the clinical trial and the informed consent process, 3) assure that the informed consent process is conducted according to the Office for Human Research Protections (OHRP) regulations and FDA guidelines and 4) comply with the National Institutes of Health (NIH) "Requirement for Education on the Protection of Human Subjects" for research investigators and key personnel involved in the research project.

C. The PI agrees to personally provide direct oversight for those responsibilities that are delegated to other staff and further assures that all individuals involved in a study have been informed about their obligations. In the absence of the PI, a sub-investigator is to be designated as responsible for the day-to-day management of the clinical research site/center. Some institutions may require personnel changes to be approved by the IRB or EC.

D. The PI accepts responsibility for study activities at any sites/centers affiliated with a main site/center. This includes assuring the quality of the data collected, subject safety and adherence to current protocols. The PI should assure that the affiliated sites/centers are conducting Quality Assurance/Control activities and that the affiliated pharmacy is visited to review the research activities.

Note: It is recommended that the PI visit all affiliated sites/centers at least annually and meet with the affiliated sub-investigators at least three times a year.

F.3. Elements of Clinical Research Site/Center Management

The DAIDS/TRP requires that each PI address these general elements in defining how the clinical research will be conducted.

Clinical Research Site/Center Administration
Staff Education and Training/Certification
Communication
Protocol Compliance Activities (Quality Assurance/Quality Control)
Regulatory Compliance
Pharmacy Compliance
Management of Laboratory Specimens
Community Advisory Board
Management Operations Evaluation

Evaluation

Staff at each site/center should develop a system for the annual review of overall clinical research site/center management functions. This evaluation should provide the opportunity to evaluate processes and procedures and allow for efficiencies to be incorporated into site/center operations.

Review

Staff from the DAIDS/TRP or designees may periodically review site/center management activities and/or visit the site/center to discuss management operations.

A copy of this plan is to be kept on file at the site/center.

F.4. Clinical Research Site/Center Management Guidelines

To better and more consistently manage the clinical research conducted at multiple sites, the Therapeutics Research Program (TRP) of the Division of AIDS (DAIDS) has developed guidance to assist staff at sites/centers in meeting management and regulatory obligations. The overall management of each site/center may vary but there are several functional areas that require close adherence to Federal regulations.

Staff at all sites/centers are required to develop a Clinical Research Management Plan that incorporates each of the **required elements** listed below. Each element must be developed in a plan for managing clinical research at a site/center. Sites/centers may vary on how they choose to implement this requirement. (The information included in the required elements is typically the type of documentation that the FDA would review during an on-site "for cause" audit).

- **Clinical Research Site/Center Administration**
- **Staff Education and Training**
- **Communication**
- **Quality Assurance (QA) and Quality Control (QC)**
- **Regulatory Compliance**
- **Pharmacy Compliance**
- **Management of Laboratory Specimens**
- **Community Advisory Board**
- **Management Operations Evaluation**

F.4.A. Clinical Site/Center Administration - Site/center files should include:

A. Organizational structure of the clinical research site/center and affiliated sites/centers, including organizational charts and job titles

B. Standard operating policies and procedures (SOPs). For example, a copy of the Table of Contents from the site/center SOP/Policy Manual could be included

C. Job descriptions for all staff

D. Documentation of annual review and assessment of staff workload/turnover

E. Copies of licenses and up-to-date curriculum vitae (CVs) of professional staff (MD, PA, RN, RPh, etc.)

F. Documentation of annual review/meeting with business/budget/fund accounting officials

G. Subject screening logs

F.4.B. Staff Education and Training -Site/center files should include:

A. Annual and continuing education/training, including annual updates, required by the site/center. A listing of required training at the site/center and the names of the individuals who attended the training is sufficient. For example, some sites/centers require annual updates on Good Clinical Practices.

B. NIH/Group/Program education/training. Names of staff members and dates when training took place along with a description of the training are sufficient. Annual updates may include typical training topics such as:

1. Orientation to the Clinical Trials Group/Program
2. Clinical Trials Group and DAIDS Policies and Procedures
3. Computer system(s)/ Electronic documentation
4. FDA Guidance for Industry and International Conference on Harmonization: Good Clinical Practice: Consolidated Guidance
5. Ongoing/new protocols
6. Orientation and evaluation of new staff
7. Proper handling and/or processing of
    a. Biohazardous materials
    b. Storage of specimens
    c. Specimen shipping
    d. Specimen tracking
8. NIH "Requirement for Education on the Protection of Human Subjects" for research investigators and key personnel involved in the research project.

F.4.C. Communication - Some or all of this information may be covered in the site/center SOPs. If that is the case, simply provide a copy of that document, supplementing where necessary. If not, site/center files should include a description of the flow/dissemination of information at the site/center, any affiliated sites/centers, the operations center, and the statistical/data management center and include; for example:

A. Staff meetings (PI/other investigators, nurses, study coordinators, pharmacists, laboratory personnel, data managers).

B. Meetings between the sponsoring site/center designee with any affiliated site/center staff.

C. Distribution of information memos, e-mails, and minutes of meetings.

D. QA/QC findings/reports.

E. Distribution of protocol-related information such as clarification memos, start-up call minutes and amendments.

F. Distribution of information from DAIDS and Clinical Trials Group/Program. For example, revised SOPs, announcements and memos.

G. Distribution of evaluation and routine performance reports from the Clinical Trials Group/Program.

H. Distribution of monitoring site visit reports.

I. Description of tools/aids developed by the site/center to document communication.

F.4.D. Quality Assurance (QA) and Quality Control (QC) - Some or all of this information may be covered in the site/center Quality Management Plan. If that is the case, simply provide a copy of that document.

Documentation of internal research record audits needs to be maintained on site and include:

A. Name of clinician responsible for QA and individual responsible for QC.

B. Description of the process for conducting QA and QC reviews at a site/center. For example: When are source documentation and protocol specific procedures for the initial subjects reviewed when a new protocol is started?

C. Copies of tools/aids that are used for implementing QC measures. Some of those listed below may not be applicable to every site/center.

1. Weekly/monthly reports
2. QC reports
3. Visit reminders
4. Data entry and transmission report
5. Error correction reports

6. Delinquency lists
7. Data retrieval programs
8. Data queries
9. Other tools/aids developed by site/center

D. QA audits - The following information shall be reviewed in the source document for every research record that is selected for initial QA review.

1. Informed consent and subject education
2. Eligibility criteria
3. Scheduled laboratory tests and procedures
4. Concomitant medications
5. Prohibited Medications
6. Drug dosing
7. AE identification and reporting
8. Clinical endpoint identification
9. Missed visit and follow-up of identified trends from the initial review

NOTE: **A minimum of 10% of the research records for each protocol shall be reviewed overall. Individual groups/protocol teams may require greater levels of QA/QC.**

E. Copies of tools/aids that are used for QA. Some of the following examples may not be used at every site/center.

1. Worksheets
2. Monthly data reports
3. Site/center evaluation reports
4. Logs
5. Summary forms
6. Monitoring site visit reports
7. Other tools/aids developed by site/center

F. Reporting QA results and documentation of QA audit findings should include:

1. Name of reviewer
2. Date of review
3. Records that were reviewed including the name of the CRFs
4. Specific contents that were reviewed in the record
5. Time period covered by the review
6. Results of review
7. Assessment of review
8. Describe how QA results are communicated to staff

G. Evaluation of the results of both QA and QC:

1. Identification of problem areas
2. Communication to site/center staff
3. Development of corrective action
4. Implementation of corrective actions
5. Evaluation of corrective actions

F.4.E. Regulatory Compliance

A. Site/center personnel will need access to:

1. US Federal Regulations: 45CFR46, 21CFR11, 50, 56 and 312
2. FDA Guidance for Industry: E6 and Good Clinical Practice: Consolidated Guidance

B. Sites/centers files need to include documentation that:

1. All study files and CRFs are: securely stored with limited access, and are available in the event of an audit by the study sponsors, local regulatory agencies and other regulatory agencies such as the FDA or designees.
2. Site/center staff are identified for maintaining regulatory files and ensuring that files are up-to-date and properly filed.
3. All required regulatory documents as listed in the DAIDS Source Documentation procedures are accessible to staff.

4. The internal process is documented for submission to the Institutional Review Board (IRB)/Ethics Committee (EC) and/or the DAIDS' Regulatory Operations Center (ROC).

5. Copies are available for tools/aids used by the site/center to track and maintain records of both IRB/EC and ROC submissions and approvals.

C. Letters or Notices of the Food and Drug Administration:

NOTICE TO NIH GRANTEES/CONTRACTORS REGARDING LETTERS OR NOTICES FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

Release Date: September 22, 2000

Notice: OD-00-053

National Institutes of Health

Many NIH grantees/contractors conduct clinical research that involves a drug, biologic or device for which there is a Food and Drug Administration (FDA) Investigational New Drug Application (IND) and/or Investigational Device Exemption (IDE). When the NIH funds all, or part, of a clinical study that is being conducted under an IND and/or IDE, it is important that the NIH be knowledgeable about any significant communications with the FDA about that study.

In order to keep the NIH informed and comply with 45 CFR 74.51 (f), the awardee institution must report FDA communications to the awarding Institute(s) or Center(s) within 72 hours of receiving (through the principal investigator or any other persons acting on behalf of the awardee) a copy of the communication or upon being informed (though the principal investigator or any other person acting on behalf of the awardee) of the FDA communication, whichever occurs first. Failure to comply with this requirement may result in corrective and /or enforcement action.

By statute, the FDA communicates with the sponsor of the IND or IDE. The sponsor may, or may not, be the NIH awardee institution or NIH-funded principal investigator. FDA regulation, 21 CFR 312.55, outlines the responsibilities of sponsors to keep each participating investigator informed during the course of the study. Thus this notice to the awarding Institute (s) and Center(s) serves to complete the information loop. Awardee institutions must immediately notify the awarding Institute(s) and/or Center(s) of any of the following communications from the FDA regarding the research.

1. Warning letters: letters that are sent to you and/or to the commercial sponsor(s)

2. Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE letters)

3. Notice of Opportunity for Hearing (NOOH)

4. Notice of Disqualification

5. Consent Agreements

6. Clinical hold letters that pertain to breaches of either Good Manufacturing Practices, Good Clinical Practices or other major issues requiring significant changes in the protocol. The notification should be made in writing, but may be done by phone, if a written notice would delay the notification. The notification shall include a statement of the action taken or contemplated and the assistance needed to resolve the situation. The awarding Institute(s) and Center(s), NIH and HHS shall, pursuant to 45 CFR 74.53, have access to the FDA communications received by the grantee/contractor and other records of the grantee/contractor that are pertinent to the grant/contract.

Web site: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html

D. Interruption of research activities due to an Office of Human Research Protections (OHRP) or Food and Drug Administration (FDA) action

1. The Principal Investigator (PI) is to notify the CRMB Program Coordinator by phone or email that an OHRP or FDA action has been initiated. A copy of the OHRP or FDA correspondence that describes the action/s that have been taken is to be faxed/emailed to the Program Coordinator.

2. The Program Coordinator is to be kept apprised or any further OHRP or FDA actions during the interruption of research activities. Copies of any correspondence that describe changes from the initial action are also to be faxed/emailed to the Program Coordinator.

E. Resumption of research activities after an OHRP or FDA action

1. The PI is to notify the CRMB Program Coordinator when the OHRP or FDA permits resumption of research activities and to advise the Program Coordinator about any special conditions required by OHRP or the FDA. A copy of the OHRP or FDA correspondence that permits research activities to continue is to be faxed/emailed to the Program Coordinator

F.4.F. Pharmacy Compliance - Site/center files shall describe how investigational products are handled. The DAIDS approved pharmacy plan that is on file at the site/center/pharmacy is sufficient to meet this requirement.

F.4.G. Management of Laboratory Specimens - Site/center files shall describe the management system for the collection, processing, storage and transportation of laboratory specimens. Reference to a site/center laboratory processing manual is sufficient for this section. If a laboratory manual is not available, this could be done with internal SOPs that describe:

A. Coordination between clinical sites/centers and laboratories and include:

1. Scheduling visits to ensure that specimens are obtained and processed based on protocol requirements
2. Proper completion of laboratory forms
3. Proper processing of specimens and shipment to outside laboratories
4. Reporting of test results
5. Correction of errors detected/reported by data/statistical centers
6. Storage conditions that provide for proper temperature, boxes, and vials

B. Periodic inventory of specimens

C. Quality of specimen management that includes:

1. Verification that the label is intact and label information is correct and legible
2. Tracking of specimens, forms, and related paperwork
3. Maintenance records and monitoring systems for freezer(s), refrigerator(s), incubator(s) and other equipment
4. Maintenance, calibration and repair records for instrumentation

D. Data capture and transfer mechanisms (e.g. software, hardcopy, logging-in, tracking, shipping, storage and error correction and updating).

F.4.H. Community Advisory Board (CAB) - A file on site shall describe the sites/centers' mechanism for incorporating CAB recommendations into the recruitment of subjects at the site/center. Most of this information is already available as part of the site/center Grant application. Include the following information:

A. Compliance with Group/Program requirements. For example, if the Group/Program has requirements for meeting attendance, are funds available for reasonable expenses, including representation at annual Group/Program meeting(s)?

B. Are CAB members representative of the HIV-infected catchment area?

C. Are CAB meetings regularly scheduled?

D. How does the staff communicate with the CAB?

E. What is the principal investigator's involvement?

F.4.I. Outreach - A file on site shall describe outreach endeavors. The inclusion of women and minorities in all aspects of site/center activities including subject recruitment and site/center staffing should be emphasized. Most of this information is already available as part of the site/center Grant application. If not, describe:

A. Subject recruitment

1. Community meetings/lectures
2. Local newspapers/radio advertisements
3. Chart review
4. Use of websites

B. Inclusion of women and minorities in activities of recruitment and site/center staffing

F.4.J. Management Operations Evaluation - A file on-site needs to describe the process of review, evaluation and revision of management operations. For example:

A. Evaluation of findings from internal QA and QC activity

B. Identification of performance areas that need improvement

C. Implementation of corrective actions

D. Periodic review of management operations to ensure staff adherence

E. Annual review of management operations for evaluation of effectiveness and needed changes

F.5. Prisoner Participation in DAIDS-Sponsored Therapeutic Clinical Trials

The SOP, "Prisoner Participation in DAIDS-Sponsored Therapeutic Clinical Trials" is divided into two sections:

Instructions for obtaining approval for prisoner participation

- Part 1. Obtain IRB approval for participation of prisoners.
- Part 2. Actions if a study subject becomes incarcerated after enrollment in a protocol.
- Part 3. Actions while research activities are suspended.
- Part 4. Actions for protocols that were NOT reviewed by an OHRP-approved IRB for prisoner participation.
- Part 5. Registration for prisoner participation.

Definitions to provide further clarification of the terms and procedures.

- A. DAIDS/TRP approval for potential prisoner participation.
- B. IRB approval of research for prisoner participation.
- C. Agreement between institutions.

If you have any questions about implementation of the SOP, please contact your CRMB Program Coordinator at (301) 496-8214.

F.5.A. Instructions

Part 1. Obtain Institutional Review Board/Ethics Committee (IRB) approval for participation of prisoners.

- Determine if the DAIDS-sponsored therapeutic protocol has been approved by DAIDS/TRP for potential prisoner participation. **Refer to Definition A. (DAIDS/TRP approval for potential prisoner participation) on page F-14.**

- Submit each protocol that has been approved by DAIDS/TRP for potential prisoner participation to the local IRB for their review and approval of prisoner participation. **Refer to Definition B. (IRB approval of research for prisoner participation) on page F-15.**

    1. The principal investigator (PI) must notify the IRB of the intent to potentially enroll or follow prisoners as study subjects.

- DAIDS/TRP recommends that all sites request IRB review and approval for prisoner participation at the IRB's initial review of <u>all</u> DAIDS-sponsored therapeutic protocols that have been approved for potential prisoner participation.

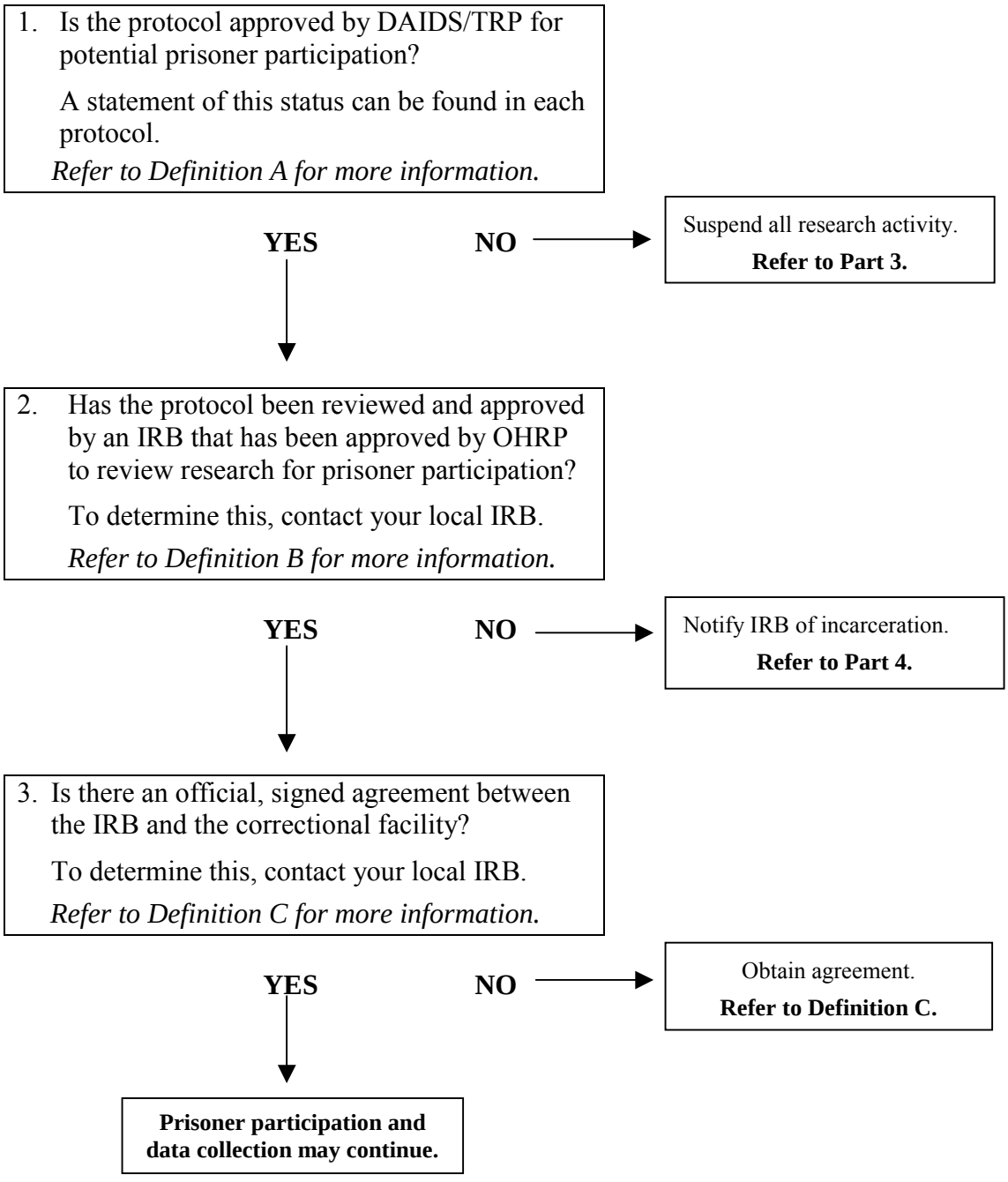
    2. The IRB should have an agreement with the prison indicating that the prison will comply with the appropriate human subjects regulations. **Refer to Definition C (Agreement between Institutions) on page F-16.**

3. If the IRB reviews the protocol and determines that it is **NOT** appropriate for prisoner participation, incarcerated subjects may **not** be enrolled or followed on the protocol by the site.

- Upon IRB approval, submit the appropriate documentation to the Regulatory Operations Center (ROC) to register for prisoner participation. **Refer to Part 5 (Registration for prisoner participation) on page F-13.**

Instructions (continued)

Part 2. Actions if a study subject becomes incarcerated after enrollment in a protocol. Follow the flow diagram below to determine what actions, if any, the site will need to take if a study subject becomes incarcerated after he or she has been enrolled in a DAIDS-sponsored therapeutic clinical trial.



Instructions (continued)

Part 3. Actions while research activities are suspended.

- The subject does not have to be permanently withdrawn from the protocol; however, data collection and efforts to contact the subject for research-related information are to be suspended.

- Investigational drugs or any study products provided by DAIDS may not be supplied to incarcerated individuals while the research is suspended.

- Incarcerated individuals who are receiving FDA-approved medications by prescription may continue to receive these medications according to policies of the prison.

- Once the subject is released from the prison, participation in the study may resume with the subject's continued consent.

Part 4. Actions for protocols that were NOT reviewed by an OHRP-approved IRB for prisoner participation, but have been reviewed and approved by DAIDS/TRP for potential prisoner participation.

- Within 5 (five) working days of becoming aware of the subject's incarceration, the PI must notify the IRB Chair in writing, that a subject has become incarcerated while on-study.

- The subject may continue on-study if the IRB Chair determines that it is in the best interest of the subject to continue in the protocol pending full IRB review. If not, research activities must be suspended—refer to Part 3 for instructions.

- The protocol must be reviewed for prisoner participation, as outlined in Definition B, at the next possible full IRB review. Refer to Definition B for information on the requirements.

- If the IRB reviews the protocol and determines that it is NOT appropriate for prisoner participation, research activities must be suspended. Refer to Part 3 for instructions.

- Upon IRB approval, the site must submit the appropriate documentation to ROC to register for prisoner participation. Refer to Part 5 for instructions.

Part 5. Registration for prisoner participation.

Submit the following to ROC for review:

1. Completed Site Registration Checklist

2. Documentation of IRB approval for prisoner participation in the form of an IRB Approval Letter that includes:

    a. The signature of IRB designee (usually the Chair or Administrator)

Instructions (continued)

b. Confirmation of the following:

(i) The prisoner representative was present during the review.

(ii) OHRP has a copy of the IRB roster on file.

(iii) The IRB determined that the required elements in Section 46.305 were met and that one of the categories in Section 46.306 permits the research to go forward.

3. A copy of the IRB-approved prisoner informed consent form

- ROC reviews and approves the completed site registration documentation required for prisoner enrollment.

- ROC registers approved sites to enroll and follow prisoners as subjects in the specified protocol.

- ROC informs OHRP of sites that are registered for prisoner participation for each DAIDS-sponsored therapeutic protocol.

F.5.B. Definitions

A. DAIDS/TRP approval for potential prisoner participation.

The Clinical Science Review Committee (CSRC) of DAIDS/TRP reviews all DAIDS-sponsored therapeutic protocols for consideration of appropriateness for prisoner participation:

1. Protocols considered for prisoner participation do not include placebos—the minimum treatment is always standard of care (as indicated by current Public Health Service guidelines).

2. Only protocols with treatment arms are considered. Observational and epidemiological studies are not approved by CSRC for potential prisoner participation.

As part of the CSRC review, RAB reviews each protocol to determine if the research is permissible for prisoner participation in accordance with:

1. 45 CFR 46.306 (a) (2) (D): "Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject." (The citation is 45CFR46.306(a)(2)(iv) in the 10-1-99 version from the Code of Federal Regulations.)

Definitions (continued)

2. The local IRB must actively document its concurrence or non-concurrence with this determination.

3. Review for compliance with 45 CFR 46.305 is **NOT** done by DAIDS/TRP—that is the responsibility of the IRB.

The final determination of approval or disapproval of a protocol for prisoner participation is made by the Associate Director, TRP and Chief, RAB. A memo documenting the review of the protocol for potential prisoner participation and the final determination of whether or not prisoners may be included is completed, signed by both parties, and forwarded to OHRP.

- A statement is included in each DAIDS-sponsored therapeutic protocol indicating whether or not DAIDS/TRP has approved it for potential prisoner participation based on 45 CFR 46.306.

B. IRB approval of research for prisoner participation.

The IRB must have approval from OHRP to review and approve research that involves prisoners.

1. If the local IRB does not have such an OHRP approval, the IRB may request it by contacting the appropriate OHRP Assurance Coordinator and submitting a revised IRB roster with a designated prisoner representative.

    a. A list of Assurance Coordinators and their assigned regions is available at OHRP's Web site: http://ohrp.osophs.dhhs.gov/dpa-staff.htm

    b. A secondary contact is the Director for Regulatory Affairs at OHRP, who is responsible for reviewing all institutional certifications related to HHS-supported research that involves prisoners.

2. The local IRB may review a study for prisoner participation in accordance with 45 CFR 46.305 without a prisoner representative IF the multicenter protocol has already been reviewed and approved for prisoner participation by another OHRP-approved IRB in accordance with 45 CFR 46, Subpart C. Contact RAB for information on this option.

The approved IRB must review the protocol for appropriateness of prisoner participation in accordance with 45 CRF 46.305 and 46.306.

The approved IRB must re-review the protocol for compliance with 45 CRF 46.305 and 46.306 if any of the following occur:

1. The protocol was not previously reviewed by the IRB for appropriateness of prisoner participation.

2. The IRB's prisoner representative was not present for the protocol review.

Definitions (continued)

The following must be documented in the IRB minutes:

1. Presence of the prisoner representative during the protocol review.

2. Approval of the protocol for inclusion of prisoners is in accordance with 45 CRF 46.305 and 46.306.

The site is responsible for maintaining records of the IRB approval for inclusion of incarcerated subjects in their regulatory files.

C. Agreement between institutions.

There should be an official, signed agreement between the IRB and the prison that states the following terms:

1. The IRB accepts responsibility for the research that is conducted in the prison.

2. The prison agrees to:

    a. The conduct of research in their facility.

    b. Comply with human subjects' protection regulations (45 CFR 46).

    c. Accept the IRB's oversight of the research.

If either institution does not agree with the terms, research activities must be suspended. Refer to Part 3 for instructions.

Prisons do not need an OHRP Assurance or need to be covered by an Institution's Assurance if they are not actively involved in the research (i.e., prison staff do not consent subjects, participate in enrollment, or conduct study visits).

F.6. Transportation of Infectious Substances

F.6.A. Air Transportation

The International Air Transport Association (IATA) has implemented regulations governing the shipping of "Dangerous Goods" via air transport. The Department of Transportation (DOT), Centers for Disease Control (CDC), and other federal agencies have regulations regarding the shipment of infectious substances. However, since the IATA regulations are more comprehensive and stringent, it is recommended that the IATA regulations be used for all domestic and international air shipments. "Dangerous Goods (Class 6)" are defined as "articles or substances that are capable of posing a significant risk to health, safety, or to property when transported by air." This classification is further divided. One of the sub-divisions is "Infectious Substances (Class 6.2)." Any specimens from subjects known to be or expected to be HIV-infected are considered to be "Infectious Substances." Thus, such specimens must be identified, marked, labeled, documented, packaged, packed, and shipped in a manner specified in the IATA regulations.

F.6.B. Surface Transport Transportation (Interstate)

- In addition to air transport, federal agencies also regulate surface transport.
- Department of Transportation (DOT) – Hazardous Materials Regulations cover highway, rail, and water transportation (49 CFR parts 100-185), and set standards for shipping contractors and shippers.
- CDC - 42 CFR 72 (Interstate Shipment of Etiological Agents) is currently undergoing revision.

F.6.C. International Shipments (Import and Export)

- CDC regulates incoming infectious substances. It requires that an importer of infectious substances from outside the United States obtain an import permit and that the importer bear responsibility for safe packing, labeling, and contact information for foreign shipping personnel. Refer to the CDC Web site for more information: http://www.cdc.gov/od/ohs/biosfty/imprtper.htm

- When shipping infectious substances to other countries, the Department of Commerce export administration regulations (15 CFR Parts 742, and 774) must be followed. Also check specific regulations in the country of destination.

F.6.D. Training Sources

- Courier as well as packaging companies offer training courses.

- National Laboratory Training Network (NLTN) is sponsored by the Association of Public Health Laboratories and Centers for Disease Control (CDC). Refer to the CDC Website for more information: http://www.phppo.cdc.gov.dls/nltn

- Other IATA accredited training courses are identified at the IATA Web site: http://www.iata.org/cargo/dg

F.6.E. Relevant Regulations/Guidelines

- CDC - 42 CFR Part 72
- Biosafety in Microbiological and Biomedical Laboratories (BMBL) 4th Edition
- DOT - 49 CFR Parts 100-185 (Hazardous Materials Regulations)
- OSHA - 29 CFR 1910.1030
- United States Postal Service, Domestic Mail Manual CO23
- IATA Dangerous Goods Regulations

F.6.F. Relevant Web Sites

- www.cdc.gov/od/ohs
- www.cdc.gov/od/ohs/biosfty/imprtper.html
- www.cdc.gov/od/ohs/irsat/42cfr72.html
- www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm
- www.osha.gov
- www.iata.org/cargo/dg
- www.text-trieve.com/dotrspa

F.7. Site/Center Closure:

These guidelines describe activities that will take place when clinical sites/centers close. These activities include: 1) subject follow-up and 2) proper disposition of drugs, study records, and specimens according to regulations and procedures of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA).

Site closure may be initiated by the Division of AIDS (DAIDS): 1) at the end or a funding period, 2) if there is a decline in subject enrollment, 3) if satisfactory standards of performance are not achieved, 4) if there is a failure to comply with regulatory requirements, and 5) if there is a failure to comply with terms of a financial agreement, if applicable.

Site closure of an affiliated site may also be initiated by the Principal Investigator (PI) of a sponsoring clinical site/center.

F.7.A. Site Procedures:

1. A letter/e-mail from the PI is to be submitted to the Program Coordinator of the Clinical Research Management Branch (CRMB). If an affiliated site/center is going to close and subcontracts or other financial arrangements are in place, the letter will need to be signed by the business officials of both sites/centers.

   The following information needs to be included in the letter:

   a. Reason for closure
   b. Proposed date of closure
   c. Status of all subjects for each protocol (on/off drug, on/off protocol, etc.)
   d. A statement about any financial arrangements, budget period commitment dates, funding mechanism (subcontract or reallocation of existing award funds), and rebudgeting need to be included, if applicable.
   e. Plan for disposition of study products, CRFs, pharmacy records and specimens

2. Any subjects still on-study may be transferred to another clinical trials site. Subjects not wishing to transfer will be discontinued from study/studies according to procedures mandated by the protocol. The Data Management Center (DMC) will turn off the randomization screens.

3. Serious adverse experiences must continue to be reported to the DAIDS Adverse Experience Report (AER) Office for sixty days after discontinuation of study drugs for those subjects who are discontinued from studies. All subject deaths are to be reported according to the DAIDS Serious Adverse Experience Manual.

4. The site/center will follow procedures for deregistration from all protocols according to the Site Registration Manual.

5. If study products are being dispensed as part of DAIDS protocols, the pharmacy will be audited after the last subject visit. All study products will be returned to the NIAID Clinical Research Products Management Center or other source. The DAIDS Pharmaceutical Affairs Branch (PAB) will oversee the return of study products.

6. Disposition of study specimens stored at the site/center will be completed before the site is closed per the Clinical Trials Group or protocol team requirements.

7. The DMC will address all data queries before site closure and all outstanding data entry must be completed before a site is closed. The sponsoring clinical site/center is responsible for resolving data queries when possible after an affiliated site/center closes. However, if a data query can only be resolved by accessing the subject's medical records residing at the closed affiliated site/center and if the staff at the sponsoring site/center do not have access or consent to review these records, the staff need to inform the DMC that the query cannot be resolved and specify the reasons.

8. A final monitoring visit will be conducted to identify any outstanding data requirements and verify disposition of all study products and specimens. The clinical site monitor will schedule a monitoring visit including a pharmacy audit, if applicable.

9. Case report forms (CRFs), including appropriate shadow files, and pharmacy records will be transferred to the sponsoring clinical site/center for storage when an affiliated site/center closes. If a sponsoring site/center is being closed, the Standard Operating Procedure for Storage of Case Report Forms and Pharmacy Records is to be followed.

10. The Regulatory Operations Center (ROC) will oversee shipment of CRFs and study records.

11. The ROC will remove the site from the clinical trials system directory.

Questions about site closure procedures should be directed to the CRMB Program Coordinator at (301) 496-8214.

F.8. Source Documentation Procedures – ***To be provided at a later date***

F.9. Essential Documentation - ***To be provided at a later date***

G. SITE MONITORING

Clinical Site/Center Monitoring

G.1. Purpose

Since the Division of AIDS (DAIDS) currently holds the Investigational New Drug (IND) Application for many of the clinical trials funded by the Therapeutics Research Program (TRP), it is our policy, as sponsor, to fully comply with obligations to monitor trials under 21 Code of Federal Regulations (CFR) 312.

The Food and Drug Administration (FDA)/International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) Guidelines Section 5.18.1. defines the purpose of monitoring clinical trials as follows:

- To verify that the rights and well-being of human subjects are protected;
- To verify that the reported trial data are accurate, complete and verifiable from the source documents; and
- To verify that the conduct of the trial is in compliance with the currently approved protocol/amendment (s), with GCP, and with the applicable regulatory requirements.

To accomplish this task, DAIDS has delegated clinical site monitoring responsibility to a Contract Research Organization (CRO) known as the Clinical Site Monitoring Group (CSMG). The CSMG will perform periodic on-site visits to sites conducting DAIDS-sponsored clinical trials and report findings to DAIDS.

Monitoring visits may be of several types including: Initiation Visits, Interim Visits, Site Closeout Visits, and Special Assignment Visits. It is anticipated that approximately 50 percent of the monitor's time on site will be directed toward an assessment of those areas of the trials that most directly affect subject safety. These include, but are not limited to, a review of: the informed consent documents and eligibility criteria, the dispensing and accountability of investigational study products, correct implementation of the protocol, internal site quality control and quality assurance procedures, adherence to Good Clinical Practice Guidelines, and a review of regulatory documentation. The additional 50 percent of the time should be devoted to an examination of source documents to assess their accuracy and completeness. This review of the data could be a verification of source documents (SD) to case report forms (CRFs) or a review of the database back to source documents. Where possible this **general guidance** will be followed; however, special assignments or other competing priorities may take precedence.

G.2. Development of Monitoring Assignments

Typically, monitoring assignments are developed quarterly. The CRMB Program Coordinators, the CSMG contractor, the Regulatory Affairs Branch (RAB), and the Pharmaceutical Affairs Branch (PAB) share the responsibility for generation of the assignments. Others that provide requests for the assignments may include the data management centers, protocol teams, or the associated Executive/Steering/Evaluation committees of the specific groups.

G.3. Interim Monitoring Visit

The typical Interim Site Monitoring Visit may include the following:

- An evaluation of the overall status of the site/center in relation to the specific assignment
- A discussion of pending issues and outstanding actions from a previous visit
- A review of protocol compliance
- A review of the Informed Consents
- A review of the status of the Investigational Product (IP)
- A review of Regulatory Compliance
- A review of the Source Documentation
- A discussion of corrective actions and administrative issues
- A debriefing for the Investigator and designated staff
- A complete documentation of all visit findings

G.4. Site Visit Report (SVR)

Each monitoring visit is fully documented in the Site Visit Report (SVR). As noted in the GCP Guidelines (5.18.4 n and q), the monitors are obligated to inform the Investigator of any Case Report Form entry, error, omission, or illegibility discovered. Additionally, the monitor must communicate any deviations from the protocol, SOPs, GCP, or regulatory requirements. As sponsor, DAIDS is required to take prompt action to secure compliance when there has been a report of noncompliance.

Actions taken following issue of final SVR:

- SVR is distributed to DAIDS staff, the Investigator of the site/center, the appropriate data management center, and possibly the Regulatory Operations Center.
- DAIDS Program Coordinators review SVRs.
- If there are no significant findings the report is filed.
- If significant findings are identified, the Program Coordinator will contact the site/center and CSMG for clarification.
- The Program Coordinators will document/ follow-up on outstanding issues and will work with the sites/centers to ensure future compliance.

G.5. Resolution of Differences

The determination and reporting of protocol violations and deviations serve two distinct purposes in DAIDS-funded trials:

1. The results of clinical site monitoring, as noted in the SVR, are **primarily** used by DAIDS as a tool for monitoring the performance of clinical trials in fulfillment of our obligations as sponsor under 21 CFR 312. As a matter of policy, research records are reviewed to determine if the protocol **as written** is being followed.

2. Additionally, the results of clinical site monitoring are also used by the cooperative groups to measure individual site performance against the performance of the Group.

Therefore, when differences in interpretation of the protocol requirements are encountered, the following procedure for a resolution will be followed:

- Both Principal Investigator (PI) and CSMG will notify CRMB Program Coordinator.
- CRMB Program Coordinator will consult with the protocol team.
- CRMB Program Coordinator will make the final decision about whether or not a protocol violation will be assigned.
- If necessary, a revised SVR will be issued.
- CRMB Program Coordinator will notify the PI and CSMG of the decision and rationale.

In terms of the overall performance evaluation as reported to the Group leadership, the PI may appeal the decision to the appropriate committee. The Group leadership may determine that the protocol violation should receive "special consideration" in their evaluation of the site's performance. It should be noted, however, that this "special consideration" of a protocol violation does not alter the decision of the CRMB Program Coordinator.

H. WORKING INSTRUCTIONS FOR SITE/CENTER OPERATIONS

H.1. Office for Human Research Protection (OHRP) Assurance of Compliance

What is an Assurance of Compliance?

An Assurance is a document approved by OHRP from a prospective awardee or other institutional performance site that will engage in Department of Health and Human Services (DHHS) conducted or supported research. It assures institutional compliance with and implementation of regulations for the protection of human subjects (45 CFR 46).

All Assurance documents include text, an IRB membership list, and a signature page. An institution is automatically considered to be "engaged" in human subjects research whenever it receives a direct HHS award to support such research. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award. See OHRP Letter dated January 26, 1999, titled Engagement of Institutions in Research under Assurance Documents, OHRP Web page. An Assurance must be in place before funds are released.

H.1.A. Types of Assurance

The Assurance Branch of the Division of Human Subject Protections routinely negotiates the following types of Assurance:

1. **Multiple Project Assurance (MPA):** is awarded to institutions that are involved in numerous federally funded research projects. Each MPA is initially approved for three-year periods and renewed for five-years.

2. **Single Project Assurance (SPA):** is limited in use and duration to an individual research activity. An activity usually consists of a single protocol but occasionally may consist of more. The Assurance and proposed informed consent documents are submitted to OHRP for detailed review and approval before award and/or involvement of subjects.

3. **Cooperative Project Assurance (CPA):** is for certain types of cooperative research (i.e., an OHRP-approved Cooperative Protocol Research Program [CPRP]). Such research often is designed to be both multi-site and multi-protocol in nature. This design brings the research to the subjects by distributing protocols widely and pooling resultant data to hasten conclusions and publication of findings. CPAs are approved for five-year periods. A CPA does not require direct review by OHRP of each specific protocol at each site before use. Instead, CPRP protocol and consent language reviews occur at the protocol design stage by OHRP or reviewers who are trained by OHRP.

4. **Agreements and Amendments**
    a. A **Non-Institutional Investigator Agreement (NIA**) is used when a CPRP performance site does not involve an institution.

b. An **Agreement for an Independent Investigator (AII)** is used when a non-CPRP performance site does not involve an institution.

c. A **Cooperative Amendment (CA)** normally is used between two or more MPA institutions (or otherwise with prior OHRP consultation) to identify circumstances and arrangements, which are jointly agreed to as suitable for reliance on one another's IRBs to avoid duplicative review efforts.

d. An **Inter-Institutional Amendment** (IIA) is used to assure compliance by a performance site without an IRB that is an affiliated performance site to an MPA institution at which employees of the MPA institution routinely conduct their DHHS research. This mechanism avoids the need for an SPA for each separate project, which is performed at such sites by employees of the MPA institution. Some MPAs have no IIAs while others have several.

5. **Application for OHRP Assurance**
   To apply for an assurance see the Web page: http://ohrp.osophs.dhhs.gov/polasur.htm and contact the CRMB Program Coordinator

6. **Assurance Renewals**
   Before the expiration date, the OHRP will send the institution a renewal application. Since investigators are responsible for conducting research under a current OHRP-approved assurance, it is incumbent upon the investigator to verify that the institution has a current, approved assurance.

For further assurance information and sample documents see the OHRP Web page at: http://ohrp.osophs.dhhs.gov/polasur.htm

H.2. Division of AIDS (DAIDS) Site Establishment Form

1. Name of the Site/Center being established.
   Address

2. Is the site that is being established a new clinical site or an affiliated site/center of a site/center that is already established?

3. If site/center is an affiliated site, what is the name of the sponsoring site/center?
   Site Name
   Address

4. What is the Health and Human Services Assurance Number assigned to this site/center to conduct clinical research that involves human subjects?

   Assurance Number_____ Expiration Date_____

5. Will prisoners be enrolled or followed?

6. Institutional Review Board responsible for this site.
   Name
   Address

7. Principal Investigator (PI).
   Name and title
   Address
   Telephone, FAX number, and Internet address

8. Investigator at this site who is responsible for the day-to-day clinical and administrative activities. A copy of the CV for the investigator is to be included with this form.
   Name and title
   Address
   Telephone, FAX number, and Internet address

9. Study coordinator at this site. A copy of the CV for the study coordinator is to be included with this form.
   Name and Title
   Address
   Telephone, FAX number, and Internet address

10. Data manager at this site.
    Name and title
    Address
    Telephone, FAX number, and Internet address

11. Name of staff member to whom all data reports (e.g., delinquency reports, unanswered queries, unresolved error reports) should be sent from the data.
Management Center (DMC)
Name
Address
Telephone, FAX number, and Internet address

NOTE: If this form is for an affiliated site/center, should data reports from the DMC go to the sponsoring clinical site designee only or both the sponsoring clinical site designee and the affiliated site/center designee?

This form is to be updated when information changes and submitted electronically to the DAIDS Program Coordinator.

H.3. Pharmacy Establishment

NOTE: This Pharmacy Plan must be completed by the Pharmacist of Record.

As a sponsor of Investigational New Drug (IND) applications, the DAIDS of the National Institute of Allergy and Infectious Disease (NIAID) must comply with the Food and Drug Administration (FDA) Code of Federal Regulations (CFR) governing the receipt, use, and disposition of investigational agents. The DAIDS has the responsibility to assure that all investigators establish and maintain adequate records of agent receipt, use, and disposition that comply with FDA regulations and the standards of research involving the use of investigational agents.

The pharmacist at each DAIDS-sponsored site, designated as the Pharmacist of Record, is the primary individual who is expected to develop and maintain an investigational agent control system, which includes the technical procedures for agent ordering, control, dispensing, and accountability. In addition, the Pharmacist of Record is responsible for the establishment of internal policies and procedures for the safe and proper use of investigational agents. The Pharmacist of Record will perform the day-to-day dispensing and accountability activities.

A pharmacy plan shall be created by the Pharmacist of Record for each clinical research site participating in DAIDS-sponsored studies, addressing the control and use of Investigational Agents. The pharmacy plan for a clinical research site must be submitted to the DAIDS Pharmaceutical Affairs Branch for approval prior to the receipt and distribution of study medication. The Pharmacist of Record is encouraged to work with other staff members on the formulation of this plan.

- If a Pharmacist of Record will be responsible for dispensing activities at more than one clinical site, provide a separate pharmacy plan for each clinical research site.
- In the event that a Site Pharmacist is responsible for the dispensing of investigational agents to subjects enrolled on protocols at other sites (hospitals and clinics), a letter describing the dispensing procedures must be co-signed by the IRB Chairman and the Director of Pharmacy at the second site. This letter serves to document the concurrence of these individuals with the proposed plan for dispensing of investigational agents to subjects at that site. This letter also serves to notify the DAIDS that all parties have been properly notified of these procedures.

The DAIDS Pharmaceutical Affairs Branch shall be informed of any procedural changes in the handling of the investigational agents, as they occur.

If there is a change in the Pharmacist of Record after the DAIDS Pharmacy Establishment Plan is approved, complete and submit the form found on page 6 of this document.

If you have any questions, contact Ana I. Martinez, R.Ph., Chief, Pharmaceutical Affairs Branch or other branch staff at 011-301-496-8213.

H.3.A. Background

1. Name, address, and site number of the clinical research site this pharmacy plan is for.

2. Name, degree, title or position, site mailing address, Internet address (if any), telephone, and fax numbers of the Pharmacist of Record who is responsible for this pharmacy plan *Note: All pharmacy-related correspondence will be sent to the contact information provided below.*

3. Shipping address where study products are to be shipped.

4. Name, degree, title or position of the back-up Pharmacist who will assume these responsibilities when the Pharmacist of Record is not available.

5. Does the pharmacy have written policies and procedures for handling investigational agents? If yes, attach.

6. Describe the system for organizing protocol information (for example, the current IRB-approved version of the protocol [and amendments if applicable], subject treatment assignment lists, order forms, packing slips, accountability records, written prescriptions, return records, letters and memos from DAIDS, Investigator's Brochures, etc.), the process for keeping this information up to date, where it will be located, and who will have access.

7. How will the Pharmacist of Record be informed of the IRB approval of a protocol? How will the Pharmacist of Record verify that s/he is working with the current IRB-approved version of a protocol?

8. How will authorized prescribers be identified for a protocol so as to prevent the unauthorized prescribing of investigational agents?

9. What procedures will be followed by the Pharmacist of Record to maintain confidentiality of a subject's pharmacy file and the investigational agent accountability records?

10. Does the pharmacy utilize a computerized investigational drug system (e.g., accountability/inventory, study information and/or medication order entry)? If so, describe.

11. Will the Pharmacist of Record be involved in subject consultation/counseling?

H.3.B. Investigational Agent Control

Each of the following questions must be answered.

1. Room Temperature Storage

    a. Where will investigational agents be stored?

    b. Who will have access to investigational agents?

    c. How will access to investigational agents be limited to only those listed in b) above?

    d. If prescriptions are prepared prior to a subject's visit, where will they be stored?

    e. Is the access limited in this storage area?

2. Refrigerated Storage in the Pharmacy

    a. Is refrigeration available?

    b. Where is the refrigerator located?

    c. How large is the refrigerator? Indicate whether cubic feet or cubic meters.

    d. Who will have access to the refrigerator?

    e. How will access to the refrigerator be limited?

    f. At what temperature is the refrigerator maintained?

    g. How often is the refrigerator monitored for temperature control?

    h. Is there documentation of the temperature monitoring of the refrigerator?

3. Refrigerated Storage in the Clinic

    a. If study agents that require refrigeration are prepared in advance for a subject's collection (pick up) at the clinic, will refrigeration be available in the clinic?

    b. How is access to the refrigerator in this area limited?

4. Freezer Storage in the Pharmacy

    a. Is a –20 to –10° C (-4 to 14°F) freezer available?

    b. If yes, where is the freezer located?

    c. How large is the freezer? Indicate whether cubic feet or cubic meters.

    d. Who will have access to the freezer?

    e. How will access to the freezer be limited?

    f. At what temperature is the freezer maintained?

    g. How often is the freezer monitored for temperature control?

    h. Is there documentation of the temperature monitoring of the freezer?

5. Minus 70°C Freezer Storage Space Availability

    a. Is –70°C freezer storage space available?

    b. If yes, where is this –70°C freezer storage space located?

    c. How many cubic feet or cubic meters are available?

    d. Who will have access to the –70°C freezer storage space?

    e. How will access to the –70°C freezer storage space be limited?

    f. At what temperature is the –70°C freezer storage space maintained?

    g. How often is the –70°C freezer monitored for temperature control?

    h. Is there documentation of the temperature monitoring of the –70° C freezer?

6. How often will the investigational agents/study drugs on the shelves and in the refrigerator/freezer be counted and compared with the accountability record? The Pharmacist of Record is required to keep complete written records (accountability records) of all investigational agents/study drugs that are received from the NIAID Clinical Research Products Management Center and of all investigational agents/study drugs that are dispensed to subjects. The count or quantity of investigational agents/study drugs that you have at your site must match the quantity on the accountability records at all times.

H.3.C. Investigational Agent Dispensing

1. An authorized prescriber listed on the FDA form 1572 must sign a written prescription at the time that a subject is registered/randomized to the protocol or when there is a change in treatment, in order for the pharmacist to dispense medications. How will the Pharmacist of Record receive this written prescription? (If electronic prescriptions are used describe this process.)

2. Describe how an initial written study medication order will be prepared and dispensed at this institution. Will these medications be prepared in the inpatient or outpatient pharmacy? (If both, describe both procedures.)

3. How will it be documented that the informed consent was signed prior to dispensing the investigational agent(s)?

4. How will the Pharmacist of Record be informed that subsequent prescriptions/refills need to be prepared? How will study agents be delivered to the subject for follow-up visits?

5. Written prescriptions must be used to notify the Pharmacist of Record when a study drug dose is changed. How will the Pharmacist of Record receive the written prescription that notifies that a dose has been changed?

6. Is a biological safety cabinet or an isolator available for preparing subjects' medications that need to be sterile?

7. How will the Pharmacist of Record dispense study agents? (check all that apply)
   ____ Directly to subjects.
   ____ Deliver study agents to other healthcare providers who will distribute it to subjects.
   ____ Through other procedures (describe).

8. How will the Pharmacist of Record receive study drugs returned by the subject? (check all that apply)
   ____ Directly from subjects.
   ____ From other healthcare providers.
   ____ Through other procedures (describe).

Pharmacist of Record Signature_____Date_____

NOTE: Pharmacy plans will not be approved without the Pharmacist of Record's dated signature and an attached copy of the Pharmacist of Record's curriculum vitae. A copy of this completed DAIDS Pharmacy Establishment Plan must be kept on file in the pharmacy.

I have on file a copy of the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Group dated_____which I have reviewed.

Signature_____ Date_____

H.3.D. Temporary / Permanent Notification of Change in Pharmacist of Record

This letter serves to notify the Pharmaceutical Affairs Branch at the Division of AIDS of a change in the Pharmacist of Record:

Permanent: _____

Temporary: _____ Date From: _____ Date To: _____

Site Name: _____ Site Number (s): _____

Name of PREVIOUS Pharmacist of Record: _____

The following information may be provided as an attachment, (see CV requirement below)

Name of NEW Pharmacist of Record: _____

Degree, Title, Position: _____

Mailing address: _____

_____

_____

Telephone number: _____

Fax number: _____

Internet address (if any): _____

Please complete the following:

_____(Initial here) I agree to comply with all of the information contained in the previous or revised Division of AIDS Pharmacy Establishment Plan. **If the pharmacy plan was revised, please attach.**

I have on file a copy of the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Group, **with the print date**: _____which I have reviewed.

Sign and date:

_____ _____

Signature of NEW Pharmacist of Record **Date**

Send:

1) This completed form, **signed and dated**
2) A copy of the **C.V.** for the New Pharmacist of Record
3) The **Revised** Division of AIDS Pharmacy Establishment Plan **(if applicable)** to:

Ana I. Martinez, R.Ph.
Chief, Pharmaceutical Affairs Branch
NIH/NIAID/DAIDS Room 5115
6700 B Rockledge Drive, MSC 7620
Bethesda, MD 20892-7620 USA
Phone: (301) 496-8213 Fax: (301) 402-1506

H.4. Quality Management Plan Annual Evaluation

Site Name:_____ Site Number:_____

The Division of AIDS requires site personnel to evaluate Quality Management (QM) Plans annually. Please complete this form and submit it electronically to the Clinical Research Management Branch (CRMB) Program Coordinator.

Quality Assurance (QA)

1. How many research records (source documents that have been compared to case report forms) have been audited during the past year for QA? Indicate the number for the main clinical site and each subsite separately.

2. Which of the following key indicators are audited in your QA process?

Informed Consents	Missed Visit documentation and follow-up	Eligibility Criteria
Regulatory Audits	Laboratory Results	Concomitant Medications
Drug Dosing	Adverse Events/Serious Adverse Events	Clinical Endpoints
Other (Specify)		

3. Which key indicators revealed a need for improvement?

Quality Control (QC)

4. What QC tools are included in your QM Plan?

5. Which tools revealed a need for improvement?

6. What percentage of case report forms are reviewed for QC prior to keying?

QM Plan Evaluation Summary

7. Has your QM plan been successful in identifying QA or QC areas in need of improvement? Yes_____ No_____
   If yes, what plans have you implemented for improvement?

8. Will you change anything in your plan for the upcoming year?
   Yes_____ No_____ If yes, what will you change?

9. How and how often were QM results communicated to staff?

10. What was done to educate and train new staff?

11. What was done to provide continuing education? How often?

12. How is it ensured that staff are appropriately qualified and trained?

13. How often did QM meetings take place where minutes were recorded?

14. Other Comments:

_____

Signature of Study Coordinator or Principal Investigator Date

H.5. Budget/Grants Management

H.5.A. GLOSSARY OF NIH GRANT TERMS

The information provided in this section is an overview of grants policy and CRMB procedures. For more detailed grants information, go to the NIH Office of Extramural Research Web page: http://grants.nih.gov/grants/oer.htm.

Budget Period: The interval of time (usually 12 months) into which a project period is divided for budgetary and funding purposes.

Competing Continuation Application (Type 2): A request for funding to renew, by one or more additional budget periods, a project period that would otherwise expire.

Consortium Agreement: A collaborative arrangement in support of a research project in which some portion of the programmatic activity is carried out through a formalized agreement between the grantee and one or more other organizations that are separate legal entities administratively independent of the grantee.

Contract Under a Grant: A written agreement between a grantee and a third party to acquire routine goods or services.

Cooperative Agreement (U01): A financial assistance mechanism used when substantial Federal programmatic involvement with the recipient during performance is anticipated by the NIH Institute or Center.

Direct Costs: Costs that can be specifically identified with a particular project(s) or activity.

Facilities and Administrative Costs: Costs that are incurred by a grantee for common or joint objectives and that, therefore, cannot be identified specifically with a particular project or program. These costs were previously known as "indirect costs," and, in most instances, will be referred to in this document as "F&A costs."

Financial Status Report (FSR): A report of expenditures required as documentation of the financial status of grants according to the official accounting records of the grantee organization. The report must be submitted for each budget period no later than 90 days after the close of the budget period.

Grant: A financial assistance mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity. A grant is used whenever the NIH awarding office anticipates no substantial programmatic involvement with the recipient during performance of the financially assisted activities.

Grants Management Officer (GMO): An NIH official responsible for the business management aspects of grants and cooperative agreements, including review, negotiation, award, and administration, and for the interpretation of grants administration policies and provisions.

Only GMOs are authorized to obligate NIH to the expenditure of funds and to make changes to approved projects on behalf of NIH. Each NIH Institute and Center that awards grants has one or more GMOs with responsibility for particular programs or awards.

Indirect Costs: Refer to definition of "Facilities and Administrative."

Key Personnel: Those individuals noted in the administrative terms included in the NGA.

New Application (Type 1): A request for financial assistance for a project or activity that is not currently receiving NIH support and must compete for support.

Non-competing Continuation Application (Type 5): A request for funding for the second or subsequent budget period within an approved project period.

Notice of Grant Award (NGA): The legally binding document that notifies the grantee and others that an award has been made, contains or references all terms and conditions of the award, and documents the obligation of Federal funds. The award notice may be in letter format and may be issued electronically.

Project Period: The total time for which support of a project has been programmatically approved. The total project period is comprised of the initial competitive segment, any subsequent competitive segment(s) resulting from a competing continuation award(s), and any non-competing extensions.

Program Official: The NIH Institute or Center official responsible for the programmatic, scientific, and/or technical aspects of a grant.

Rebudget: To transfer funds from one budget category to another, e.g., to move funds from the budget category "equipment" to the budget category "personnel."

Restricted Funds: Portions of an award may be restricted either for use for a specific purpose only or are restricted pending the receipt of information or documentation.

Terms and Conditions of Award: All legal requirements imposed on a grant by NIH, whether based on statute, regulation, policy, or other document referenced in the grant award, or specified by the grant award document itself. The Notice of Grant Award may include both standard and special conditions that are considered necessary to attain the grant's objectives, facilitate postaward administration of the grant, conserve grant funds, or otherwise protect the Federal Government's interests.

Total Project Costs: The total allowable costs (both direct costs and facilities and administrative costs) incurred by the grantee to carry out a grant-supported project or activity. Total project costs include costs charged to the NIH grant and costs borne by the grantee to satisfy a matching or cost- sharing requirement.

Unobligated Balance: Unexpended funds at the end of a given budget period.

Withheld Funds: A portion of a grant award may not be awarded at the beginning of a budget period for various reasons such as poor performance or lack of required information. Funds may be awarded later in the budget period, if the problem is resolved.

U01: A U01 Award is a Research Project Cooperative Agreement. This award is used to support a discrete, specified, circumscribed project to be performed by named investigators in an area representing specific interest and competencies.

H.6. Storage of Case Report Forms and Pharmacy Records

PURPOSE
This standard operating procedure (SOP) describes the procedures for storage of case report forms (CRFs) and pharmacy records for the Division of AIDS (DAIDS) sponsored clinical trials at DAIDS/TRP-sponsored sites that close. This procedure should be utilized at the end of the site's phase-out period.

POINT OF CONTACT
DAIDS, Regulatory Affairs Branch (RAB) is responsible for the management of this SOP. The Regulatory Operations Center (ROC) is responsible for receiving and re-packing CRFs and pharmacy records for storage at the Washington National Records Center (WNRC). The Records Coordinator at ROC is the contact person, and may be reached at (301) 770-4550.

OBJECTIVES
As sponsor, DAIDS/TRP provides storage for CRFs and pharmacy records at WNRC for DAIDS/TRP-sponsored clinical sites that close. These records must be organized and stored by protocol and subject should there be a need for future retrieval.

SCOPE
Only CRFs and pharmacy records from DAIDS/TRP-sponsored clinical trials will be stored at the WNRC. DAIDS/TRP will only provide this service to clinical sites that close.

RESPONSIBILITY
The Principal Investigator (PI) is responsible for appropriately managing the storage of research and regulatory records when a site/center closes.

H.6.A. PROCEDURES

Identifying records for storage:

- What to send:
    1. Case report forms
    2. Pharmacy records

- What not to send:
    1. Signed informed consents
    2. Copies of protocol
    3. Site registration records
    4. Regulatory documents (Examples of regulatory documents include but may not be limited to Institutional Review Board/Ethics Committee approvals for protocols, amendments and informed consents; official notices from the DAIDS, Protocol Team, Site Registration Office, data managers and monitors; and documentation from the PI to any of the above. Also, all pertinent research correspondence [e.g., e-mail messages, faxes, and letters]).

NOTE: Study documents (1 through 4), as noted above, must be maintained at the site for three years after the site/center has closed.

5. The original research records, clinic notes, and hospital notes are kept on site and preserved according to institutional policy.

H.6.B. Packing CRFs and Pharmacy Records for Storage by DAIDS/ROC:

1. Use strong packing boxes that will not break during shipping.
2. Remove each subject's CRFs from the notebook binder and place intact in manila folders or bind them in such a way that the forms do not tear or become dislodged during shipping.
3. Keep the Subject Identification (PIDs) in numerical order when packing the CRFs of each protocol.
4. Pack pharmacy accountability records in a separate folder or envelope. The pharmacy records should be bound separately, well identified and included either at the front of the first box or the back of the last box. The study coordinator should work with the site pharmacist to determine how and when the packing should take place.
5. Send all CRFs for a protocol in one shipment. It is important not to split the CRFs of one protocol between two separate shipments. It is acceptable to send several protocols in one shipment.
6. Include the following information IN EACH BOX:
    a. Name and number of the site/center or affiliated site/center;
    b. Name of the PI;
    c. Protocol number(s) that are packed in that box;
    d. Complete list of PIDS, by protocol, in numerical order; and
    e. A copy of the master list (see number 7 below).
7. Send the same information printed on a master list (composite list of all information in all of the boxes of each shipment) to the Records Coordinator at ROC, and retain a copy for the PI's files (to be kept for a period of three years). Also include the master list inside each box. Box lists and master lists are important in case the shipment is partially or completely lost.
8. Contact the Records Coordinator at ROC to receive permission to send the boxes to ROC.
9. Dispatch the shipment so that ROC will receive the boxes on a workday (never on a weekend or holiday).

H.6.C. Shipping CRFs and Pharmacy Records

1. The site is responsible for shipping costs.
2. Number each box in the following manner:
    a. The number of the particular box and the total number of boxes sent in that mailing. For example: 5 of 8. This indicates box number 5 in a shipment of 8 boxes.
    b. The placement of this number, 5 of 8, should be on the ends or sides of the box, not the top or bottom

3. Send the boxes by UPS, Parcel Post, Federal Express, or other carrier to:

Records Coordinator.
Regulatory Operations Office
6101 Executive Blvd., Suite 200
Rockville, MD 20853
(301) 770-4550

4. Notify the Records Coordinator at ROC of the expected arrival date of the boxes and the number of boxes that have been sent.

5. The Records Coordinator will send a message back to the site/center when the boxes arrive at the ROC.

H.7. Abbreviations and Acronyms

NIH and Related Research Organizations

AACTG	Adult AIDS Clinical Trials Group
ACTIS	AIDS Clinical Trials Information Service
ARAC	AIDS Research Advisory Committee
ATIS	AIDS Treatment Information Service
BSP	Basic Sciences Program
CDC	Centers for Disease Control and Prevention
CPCRA	The Terry Beirn Community Programs for Clinical Research on AIDS
CRMB	Clinical Research Management Branch
CSMG	Clinical Site Monitoring Group
CSRC	Clinical Science Review Committee
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FIC	Fogarty International Center
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
MACS	Multicenter AIDS Cohort Studies
MSG	Mycoses Study Group
NAAIDC	National Advisory Allergy and Infectious Disease Council
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
OAR	Office of AIDS Research
OHRP	Office for Human Research Protections
PACTG	Pediatric AIDS Clinical Trials Group
PHS	Public Health Service
PAB	Pharmaceutical Affairs Branch
RAB	Regulatory Affairs Branch
ROC	Regulatory Operations Center
SOCA	Studies of the Ocular Complications of AIDS
TRP	Therapeutics Research Program
VPRP	Vaccine and Prevention Research Program
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study

Other Acronyms

AE	Adverse Event/Experience
AER	Adverse Experience Report
AIDS	Acquired Immunodeficiency Syndrome
CAB	Community Advisory Board

CCG	Community Constituency Group
CFR	Code of Federal Regulations
CRF	Case Report Form
CS	Concept Sheet
CTA	Clinical Trials Agreement
CTAAG	Clinical Trials At A Glance Report
CTS	Clinical Trials Specialist
EC	Ethics Committee
FY	Fiscal Year
GCP	Good Clinical Practice
GCRC	General Clinical Research Center
GLP	Good Laboratory Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IoR	Investigator of Record
IRB	Institutional Review Board
LFU	Lost to Follow-up
LOU	Letter of Understanding
MM	Medical Monitor
MO	Medical Officer
MOOP	Manual of Operations
MOU	Memorandum of Understanding
NCAB	National Community Advisory Board
NDA	New Drug Application
NWCS	New Work Concept Sheet
PC	Project Coordinator
PI	Principal Investigator
PID	Patient/Subject Identification Number
PLWA	Person Living With AIDS
PSR	Protocol Status Report
PWA	Person With AIDS
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
QoL	Quality of Life
RFA	Request for Applications
RFP	Request for Proposals
SAE	Serious Adverse Event/Experience
SID	Study Identification Number
SOP	Standard Operation Procedure

H.8. Glossary of Research Terms

Affiliated Site/Center: A site/center that is sponsored by another site/center that is already a member of a clinical trials group.

Clinical Research Site/Center: A place where subjects are evaluated and treated according to a research protocol.

Coordinating Center: A central unit responsible for receipt and distribution of information and/or clinical trials materials.

Data Manager: The person responsible for the management of clinical data. This includes, but is not limited to: 1) collecting, maintaining, and monitoring clinical trial data, 2) organizing and preparing weekly study forms, study spreadsheets, laboratory requisitions, and other materials required by the protocols, 3) implementing quality measures including the regular review of study and medical records, 4) evaluating and ensuring the accuracy and completeness of subject data, 5) assisting the data monitoring staff at the Data Management Center in verifying, correcting, or obtaining data, and 6) transferring data to the Data Management Center/Statistical Center.

Investigator of Record: The physician designated by the PI who is responsible for ensuring that a specific clinical investigation is conducted according to the obligations stated in the signed Statement of the Investigator, Food and Drug Administration (FDA) Form 1572, the regulations governing the rights, safety, and welfare of subjects who are participating in a clinical investigation and the policies for control of investigational drugs. The PI may also act as the IoR when the PI is the physician responsible for the conduct of a specific investigation.

OHRP: The Office for Human Research Protections (OHRP) is an office at the Department of Health and Human Services (DHHS) responsible for regulations pertaining to protecting human subjects in biomedical and behavioral Research. The office is located in the Office of the Assistant Secretary for Health. OHRP's functions include implementation of the DHHS Regulations for the Protection of Human Subjects (45 CFR 46), and the provision of guidance on ethical issues in biomedical or behavioral research.

Pharmacist of Record/Site Pharmacist/Drug Manager: The Site Pharmacist is the primary individual who is expected to develop and maintain an investigational drug control system, which includes the technical procedures for drug ordering, control, dispensing, and accountability. In addition, the Site Pharmacist may be expected to assist in 1) preparation of blinded study agents, 2) development of special dosage forms and packaging, 3) drug compliance monitoring of subjects, 4) preparation of drug information/data sheets for pharmacy, nursing, and other personnel, 5) data collection and documentation; and 6) development of research protocols.

Principal Investigator: The individual responsible for all research activities at the clinical site/center and any affiliated site/center. The PI has the authority to approve or disapprove any new research activities. The PI delegates all clinical and administrative tasks as needed, communicates information and oversees site/center management and staffing concerns. The PI oversees the conduct of each specific protocol or delegates management responsibility for a specific protocol to another physician known as the Investigator of Record (IoR). The PI will

disseminate protocol information to affiliated clinical sites/center; and ensure serious adverse experiences are reported to the Regulatory Operations Center).

Program Coordinator: The individual at DAIDS who acts as the liaison between the site/center personnel and the Division of AIDS.

Quality Assurance: The process of retrospectively reviewing the various components of the research process to assess the adherence to policy and procedure and determine the accuracy of the entire research record. For example, staff will evaluate key components of source documentation and compare them with completed case report forms. It is a periodic process, for a defined sample, for a defined period.

Quality Control: The ongoing, day-to-day process of checking case report forms for logic and completion. For example, are all headers completed? Do the dates match? Are all required areas completed? QC measures do not constitute QA but are a critical piece of the Quality Management Plan. Quality control measures are concurrent, 100percent, and carried out on all samples.

Quality Management: The overall process that incorporates both Quality Assurance (QA) and Quality Control (QC) activities into a planned and systematic program that is communicated to all staff, documented, and evaluated for effectiveness.

Regulatory Operations Center (ROC): The Regulatory Operations Center manages regulatory responsibilities for DAIDS-sponsored trials. This includes 1) Investigational New Drug Submissions, 2) Site Registration processing and review, 3) receipt and review of Serious Adverse Experience Reports and submission to the Food and Drug Administration, and 4) maintenance of regulatory files.

Research Clinician: The Research Clinician (e.g., R.N., N.P., P.A., M.D.) is responsible for directing the care of subjects enrolled in DAIDS-sponsored trials within the context of specific protocol guidelines. This may include but is not limited to 1) interviewing and examining subjects, 2) providing subject care and education about the protocol and matters related to disease course, 3) completing case report forms (CRFs), 4) maintaining subject files, and 5) obtaining follow-up information.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of a trial. Source data are contained in source documents (original record or certified copies). Source data include medication histories, medical histories, verification of eligibility, protocol compliance/noncompliance, adverse events/complications, etc.

Source Document: Original documents, data, and records where information regarding subjects is "first" recorded. Investigator subject files or hospital records generally are the basis of source document information. The information in the source documents is used to complete the case report forms.

Source Documentation: All written and printed source documents that are pertinent to a research subjects' exposure to the investigational agent(s), exposure to other treatments, progress of disease course, and response to therapy. These may include any record of a subject's condition during participation in a research study, including but not limited to the following: hospital charts, clinic notes, X-ray and laboratory reports, consult notes, and letters.

Study Coordinator/Project Coordinator: The Study Coordinator is responsible for managing and coordinating the clinical research projects of the clinical site and works closely with the PI and the Research Nurses to ensure proper subject recruitment and protocol implementation. The coordinator establishes and coordinates systems and communication channels between the clinical site and support facilities. The coordinator is the liaison for the investigators, the Data Management Center/Statistical Center, and the Operations Center.

Co/Sub-Investigators: In the event that a clinical trial is conducted by a group of clinicians, the PI or the IoR is viewed as the team leader and the associated physicians, physician's assistants, nurse practitioners, and pharmacists are viewed as sub-investigators. All clinicians with prescribing authority should be listed on the FDA Form 1572, box 6.

H.9. Contact Information 2000

DAIDS Clinical Research Management Branch (CRMB)
Main Telephone: (301) 496-8214 FAX: 301-480-4582

CRMB Branch Chief - Fred Batzold
Telephone: (301) 402-0143 Email: fb10c@nih.gov

CRMB Staff:

Adult ACTG Program Coordinator - Margaret (Peg) Rodgers-McKenna
Telephone: (301) 402-1308 Email: ma16g@nih.gov

Pediatric ACTG Program Coordinator – Karen Reese
Telephone (301) 496-7124 Email kr54d@nih.gov

CPCRA Program Coordinator - Judith Brooks
Telephone: (301) 496-7122 Email: jb359r@nih.gov

AIEDRP Program Coordinator – Glenn Sturge
Telephone (301) 402-1500 Email: gsturge@nih.gov

Clinical Site Monitoring Project Officer - Pamela Scanlan
Telephone: (301) 496-0701 Email: ps27s@.nih.gov

Financial Management Specialist - John Brooks
Telephone: (301) 435-3764 Email: jb443w@nih.gov

Program Analyst - Annice Bergeris
Telephone (301) 402-3221 Email: ab31a@nih.gov

Clincial Program Coordinator - Mieko Meshiro
Telephone: (301) 402-2307 Email: mm227q@nih.gov

Statistical and Data Management Center (SDAC) Program Coordinator – Peter Gilbert
Telephone: (301) 402-3224 Email: pg18p@nih.gov

Special Projects and DAIDS CCG Liaison - Margaret Matula
Telephone (302) 402-2302 Email: mm154j@nih.gov

Special Projects - Karen Oseekey
Telephone: (301) 402-3222 Email: ko28j@nih.gov

DAIDS Pharmaceutical Affairs Branch (PAB)
Main Telephone: (301) 496-8213 FAX: (301) 480-5703

For questions about status of drug order, drug supply and product information.
Telephone: (301) 294-3453 FAX: (301) 294-2905

DAIDS Regulatory Affairs Branch (RAB)
Main Telephone: (301) 435-3741 FAX: (301) 402-1506

Site Registration
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Serious Adverse Experience Reporting Office
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